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Ultrasound-Guided Supraclavicular Block in a Patient with Fahr Syndrome

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Zeynep Nur AKÇABOY[3]

INTRODUCTION

Fahr Syndrome (FS) is a rare disease where calcium and other minerals are bilaterally and symmetrically stored in basal ganglia, cerebellar dentate nucleus and white matter. Genetic, metabolic, infectious conditions are included in the etiology. It is characterized by extrapyramidal and neuropsychiatric symptoms. Treatment is symptomatic treatment to improve calcium metabolism (Calili et al., 2016: 1029-1031). In this case report, we aimed to share our supraclavicular block experience in a patient with FS for 8 years.

CASE

An operation for the 5th finger proximal phalanx fracture was planned to a 48-year-old, 80 kg patient having FS for 8 years. There were dementia, involuntary movements in his hands at nights, cough after fluid intake and incontinence in his history. In the preoperative evaluation, physical examination revealed apathy, gait and balance disorder, dysarthric speech, ataxia, cerebellar dysmetria and ptosis in the left eye (Figure 1). He was using 1 * 1 amantadine sulfate (PK-Merz 100 mg tablets. Assos Pharmaceuticals, Turkey), 2 * 1 carbamazepine (Tegretol 200 mg tablets. Novartis Health, Turkey), 1 * 1 modafinil (Modiwak 100 mg tablets. Generica Pharmaceuticals, Turkey), 1 * 1 baclofen (Lioresal 10 mg tablets. Novartis Pharmaceuticals,Turkey). Tested blood values and hormonal-metabolic profile were normal. The preoperative Calcium (Ca) value was 9.7 mg/dL. Cranial tomography showed hyperdense regions in bilateral caudate nucleus, globus pallidus, thalamus and cerebellar hemispheres (Figure 2). Continuation of the existing treatment was recommended by the neurology department. The patient was taken to the operation room, followed by standard monitoring (electrocardiogram, pulse oximetry and noninvasive blood pressure) and intravenous (IV) access provided from the right hand. Patient received 4 L/min oxygen with a mask and sedation provided by IV 0.03-0.05 mg / kg midazolam (Dormicum, Roche). In supine, bedside up position, disinfection done and block area covered with sterile drapes. 3 cc 2% lidocaine HCl (Aritmal, Biosel) applied subcutaneously. The 10-18 MHz linear ultrasound (EsaoteMyLab 30, Geneva, Italy) probe was placed on the clavicle in the coronal oblique plane. At the same time, a peripheral nerve stimulator (Stimuplex®Dig-B-Braun) at 1 mA current and frequency of 2 Hz was used to determine the localization of the nerves to be blocked. 18 gauge 50 mm needle (Pajunk, Geisingen, Germany) was entered with the inplane technique and the subclavian artery was detected on the first costa. Needle image was continuously displayed during operation.

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When the motor response of the nerve stimulation (fingers, wrist and elbow extension) was seen, the stimulator current was reduced to 0.4 mA. A mixture of 15 ml of 0.5% bupivacaine hydrochloride (Marcaine 0.5%, Astra Zeneca) and 10 ml 2% lidocaine HCL was slowly injected after observing the negative aspiration of blood and also observing that in every 5 ml. Local anesthetic was applied to surround the entire plexus. The patient developed sensory block and complete motor block at 15th minute and operation lasted 1 hour. Intraoperative Ca control value was 9.4 mg/dL. The patient did not need opioids in the intraoperative period and also did not need any analgesic for 10 hours postoperatively

DISCUSSION AND CONCLUSION

FS is a rare neurodegenerative disease with symmetrical bilateral calcification in the basal ganglia, caudate nucleus and cerebral cortex. It is an insidious and progressive disease and becomes symptomatic in the 4th and 6th decades of life. The late-onset type usually begins at the age of 50 and is characterized by progressive dementia and movement disorders. Diagnosis is made by cranial tomography. The treatment is symptomatic and antipsychotics, antidepressants, antiepileptics and procognitive drugs are used (ALEMDAR, 2018: 206-208; Jaworski et al., 2017: 490-493). As a matter of fact, the diagnosis of our patient was based on bilateral symmetric calcification in cranial tomography taken due to movement disorders and progressive dementia. Patient's complaints had started with walking and balance disorder and had progressed with speech disorder, ataxia, cerebellar dysmetria, dementia and incontinence.

The physical condition, comorbidities, type and duration of surgery are effective in the selection of anesthesia type for patients having Fahr syndrome. Choice of anesthesia can be general or regional. The most important aim of anesthesia management is to prevent metabolic disorder caused by plasma Ca concentration. In general anesthesia, difficult airway and malignant hyperthermia should be considered. Also for regional anesthesia it should be noted that cardiotoxicity potential of bupivacaine may increase in the presence of low Ca levels (Gupta & Lalit Gupta, 2018: 1-6).

When the literature for anesthesia applications in patients with Fahr syndrome is examined, the general anesthesia approach (Belenli & Arpaci, 2014) is mentioned in the case of Belenli et al. , but no cases have been reported under peripheric regional anesthesia. In this respect, we think that our case is the first. The reason we preferred regional anesthesia with supraclavicularvular block was that we could detect the epileptic seizure more easily in the awake patient and could intervene urgently. At the same time, we aimed to decrease the possibility of pain and stress related seizures by continuing analgesic activity in the postoperative period.

As a result, the regional anesthesia application in FS patient may be a good choice in terms of reducing the complications such as seizures due to its anesthetic and analgesic activity in intraoperative and postoperative periods.

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Figure 1: *Pitosis at left eye*

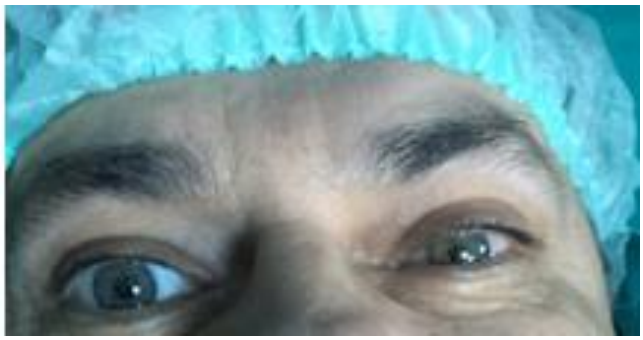
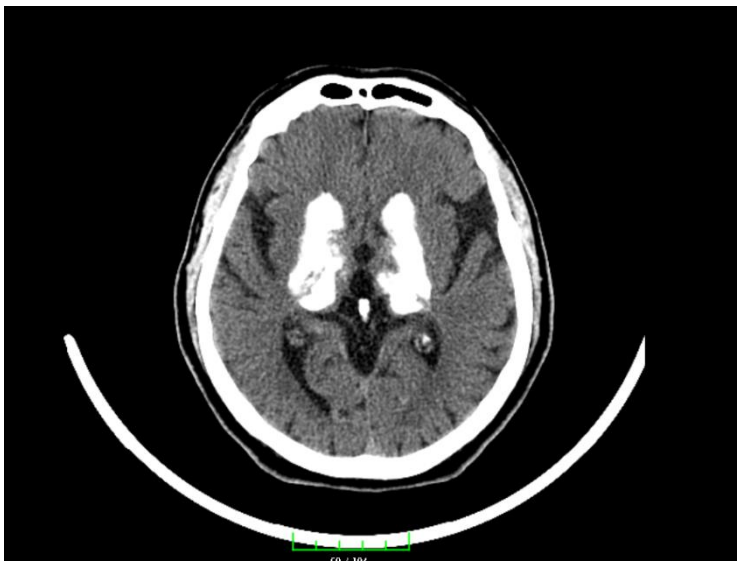


Figure 2: *Calcification in bilateral caudate nucleus, globus pallidus, thalamus and cerebellar hemispheres on cranial tomography*



Public Perceptions Towards Bariatric Surgery

Damla SEÇKİN[1]

Introduction

Bariatric surgery is an important treatment option for obesity, a chronic disease, and the improvement of many comorbidities associated with obesity. Despite the proven effectiveness of surgery in achieving long-term weight loss and significant improvement in comorbidities, a large portion of obese patients do not undergo surgery. The reasons for this include economic problems, the complexity of the bariatric surgical process, and societal perception (Rajeev et al., 2023). It is of great importance to determine the perception of communities regarding bariatric surgery. Therefore, this study aims to compile the literature on the community's perception of bariatric surgery. The study was planned as a literature review. PubMed, Google Scholar, Ebscohost, and Web of Science databases were used in the research. Keywords such as "bariatric/obesity surgery," "public perception," "obesity," and "view" were scanned.

Bariatric Surgery and Public Perceptions

There are more than 1.9 billion people affected by obesity worldwide, and the prevalence of obesity continues to increase. The reasons for the widespread occurrence of obesity include changing work conditions, sedentary lifestyles, transportation patterns, urbanization, increased consumption of high-fat and high-sugar foods, and environmental and societal changes (World Health Organization, 2021). As the number of individuals with obesity rapidly increases, the treatment options for obesity become crucial. Medical nutrition therapy, exercise therapy, behavior change therapy, pharmacological treatment, and surgical treatment are among the treatment options for obesity (Ministry of Health, 2017). Among these options, bariatric surgery is the most effective treatment method.

Bariatric surgery encompasses various surgical procedures such as sleeve gastrectomy, Roux-en-Y gastric bypass, duodenal switch, and adjustable gastric band. After surgery, patients not only experience significant weight loss but also get rid of many comorbidities such as diabetes, hypertension, and dyslipidemia.

Postoperative weight loss depends on factors such as the type of surgery, the patient's eating habits, and additional health conditions. Weight loss peaks in the first year and slows down or stabilizes at 1.5-2 years. Patients who undergo sleeve gastrectomy are expected to lose approximately 55-80% of their excess weight in 1-1.5 years. In Roux-en-Y gastric bypass surgery, this percentage ranges from 60-85%. In addition to weight loss, surgeries also provide metabolic improvements. The impact of bariatric surgery on diabetes is highly positive. After surgery, patients are able to discontinue insulin or medication use and overcome diabetes. Surgery also leads to improvement in conditions such as hypertension, dyslipidemia, sleep apnea syndrome, gastroesophageal reflux, joint disorders, and polycystic ovary syndrome, which affect various systems and organs of the body (Asad, 2022; Dana Telem, 2023; Hua et al., 2022; Thereaux et al., 2018).

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Despite all these achievements, the bariatric surgery process is complex, and there is a lack of knowledge among the public about the process and the surgery itself. In a study conducted in Kocaeli, Turkey, the aim was to inform individuals with a BMI >30 kg/m2 about bariatric surgery. Most of the patients (84.9%) reported having heard of bariatric surgery as a treatment option, but they stated that they did not know the details, techniques, and risks of this method. When asked about the sources of information on obesity surgery, it was stated that the main source was television (76.1%), and only 4.1% of patients had seen an informative brochure on this subject (Güler et al., 2018).

There is a negative societal perception regarding the reliability and effectiveness of bariatric surgery. A systematic review revealed that while some participants were aware that bariatric surgery leads to weight loss, improves comorbidities, and enhances quality of life, a significant portion of participants considered bariatric surgery unsafe and risky. The study emphasizes that the perception of bariatric surgery varies based on factors such as race, region, gender, and age. Furthermore, the research highlights that female patients have more positive perceptions and expectations regarding bariatric surgery. It is noted that there is a misconception and lack of information in the society regarding bariatric surgery (Afonso et al., 2010; Lee et al., 2019; Rajeev et al., 2023).

Studies have shown that bariatric surgery is not perceived as a medical procedure by the public, and there is inadequate information about its safety and effectiveness, indicating a misconception about the surgery (Lee et al., 2019; Zhang et al., 2022). The lack of knowledge among patients about bariatric surgery may lead them to avoid considering it as an option for obesity treatment. This can be a significant barrier for patients who genuinely need bariatric surgery as a treatment option.

Approximately 20% of obese individuals in society perceive bariatric surgery as risky (Prasad et al., 2020). Moreover, around 58% of obese individuals have seen bariatric surgery as a highly effective option for weight loss (Huq et al., 2020). It is also mentioned that there are expectations regarding bariatric surgery's ability to improve comorbidities and quality of life. However, the proportion of these individuals is quite low due to their lack of awareness of the negative impact of obesity on their health (Murtha et al., 2022; Nickel et al., 2018). Standardized educational materials and patient information are of great importance to shape the perceptions of obese individuals regarding bariatric surgery during the preoperative period.

Considering all these factors, the information gap among patients can lead them to avoid seeing bariatric surgery as a treatment option for obesity. This can pose a significant obstacle for patients who truly need bariatric surgery as a treatment option.

Positive perception of a particular treatment is one of the fundamental criteria for affected individuals to seek that solution. Factors such as education level, social media and print media, peer or environmental experiences, and many others can influence the public's views on bariatric surgery. Print media is an important factor in shaping the public's views on bariatric surgery since negative news disrupts the general awareness of bariatric surgery. Unfortunately, most of the information sources about bariatric surgery for patients are non-medical sources. While these sources increase the awareness of treatment methods, they also lead to individuals being misinformed or having insufficient information (Güler et al., 2018).

In a study conducted in Denmark, nearly half of the participants argued that due to their perception of bariatric surgery, the costs of the operation should be covered by individuals themselves, not the state. People's beliefs about bariatric surgery are an important determining factor in their views on treatment. The study concludes that the German public is quite cautious about bariatric surgery. Despite the increasing number of surgeries, it can be assumed that

misconceptions regarding the effectiveness and risk models of bariatric surgery are still widespread (Sikorski et al., 2013).

In a study conducted in China, university students were asked questions about bariatric surgery. The study found that the students had a low acceptance rate for undergoing the surgery and expressed concerns about the complications associated with the procedure. When faced with surgical options, the students did not demonstrate a positive attitude towards undergoing the surgery (Diao et al., 2022).

In conclusion, although there is a widespread negative perception of bariatric surgery in society, addressing the lack of information and educating the public through various methods will help shift the perception towards a more positive view of bariatric surgery.

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Aortıc Aneurysms And Dıssectıon

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Introduction

We desired to present an overview of the aneurysm and dissection of the largest artery of our body, the aorta, which carries blood from the heart to all organs, which is of critical importance and is seriously mortal when admitted to the emergency department (ED).

Aortic Anatomy

The aorta is the largest artery in the body. It consists of 5 main parts (Collins, Munoz, Patel, Loukas, & Tubbs, 2014):

1) Root or sinus segment extending to the sinotubular junction in the aortic valve

2) The ascending thoracic aorta extending from the sino-tubular junction to the innominate artery

3) Aortic arch extending from the innominate artery to the left subclavian artery

4) The descending thoracic aorta extending from the left subclavian artery to the diaphragm

5) Abdominal aorta extending from the diaphragm to the aortic bifurcation

The aortic wall consists of three layers: inner thin intima, thick central media, and outer thin adventitia (Collins et al., 2014).

What is an Aneurysm?

In rough terms, it is the formation of a sac due to the regional enlargement of a part of the aorta. This enlargement is crucial because it prepares the ground for the aorta rupture. While it is defined as an enlargement of up to 1.5 times the standard diameter for the abdominal and descending thoracic aorta (Johnston et al., 1991), it is not appropriate for the aortic root and ascending thoracic aorta. For the ascending aorta, a diameter of $\geq$ 4.5 cm is called an aneurysm (Paruchuri et al., 2015). Diagnosing an aneurysm early and following up on the patient's aneurysm by arranging treatments is essential. Because although the aneurysm may not cause a problem on its own, its mortality is very high when it ruptures. The location and size of the aneurysm are of critical importance. For example, An ascending aortic diameter of 4-4.4 cm increases the risk of dissection 89 times, while $\geq$ 4.5 cm causes it to increase 348 times (Paruchuri et al., 2015). Therefore, there is a correlation between the size of an aortic aneurysm and dissection, and clinicians should approach patients with this in mind.

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What is Aortic Dissection?

Aortic dissection, which is rarely admitted to emergency departments but is mortal, is the formation of an intimal tear that allows blood to pass by, creating a flap that divides the intima longitudinally and separates the true lumen from the newly formed false lumen. Aortic dissection is the most common of the acute aortic syndromes (Clough & Nienaber, 2015). The dissection flap may show an antegrade or retrograde location. It can cause life-threatening conditions such as myocardial ischemia, cardiac tamponade, acute stroke, and acute aortic regurgitation. Aortic rupture occurs when blood in the false lumen ruptures the tunica media and adventitia. The incidence of aortic dissection is estimated to be 5-30 cases per million people per year. Some genetic features and comorbidities increase this rate. It is more common in men. Although it may occur earlier in patients with Marfan, Ehlers–Danlos syndrome, it is usually seen between 50-70 (Clough & Nienaber, 2015).

A new definition was developed in 2020, after the traditional definition, which was accepted as acute in the first two weeks after the onset of the most common symptoms, such as back pain, chest pain, and abdominal pain, and chronic after > two weeks. According to this definition, the first 24 hours were considered hyperacute, 1-14 days acute, 15-90 days subacute, and >90 days chronic (Booher et al., 2013).

Acute dissection of the ascending aorta is quite mortal in untreated patients. Patients who develop cardiac tamponade, acute myocardial infarction, and stroke have a higher risk of death. Therefore, surgical or endovascular interventions, which are absolute treatments, should be applied immediately (Tsai, Nienaber, & Eagle, 2005).

Aortic Dissection Classification

Basically, two classifications have been used for years: DeBakey and Stanford.

It is categorized as type 1,2,3 according to the DeBakey system (De Bakey et al., 1965).

Type 1: Originates from the ascending aorta. It extends distally to include the arcus aorta and the descending aorta.

Type 2: Limited in the ascending aorta.

Type 3: Originates from the descending thoracic aorta and usually extends distally.

Type 3A: Limited to the descending thoracic aorta only.

Type 3B: Extends from the descending thoracic aorta to the diaphragm.

According to the Stanford system, it is categorized as types A and B according to whether it involves the ascending aorta, regardless of its origin (Daily, Trueblood, Stinson, Wuerflein, & Shumway, 1970).

Type A: All dissections involving the ascending aorta

Type B: All dissections from the arcus aorta without the ascending aorta

Imaging of the Aorta

Aortic imaging can be performed with computed tomography (CT), magnetic resonance imaging (MRI), transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and abdominal aortic ultrasonography (US). Many factors, including hemodynamic stability, contrast allergy, renal function, and patient tolerance, play a role in selecting imaging

modalities (Beebe et al., 2000). However, as it is known, the most common and detailed imaging method in emergency departments is CT (T.-L. C. Lu et al., 2009).

A) CT: It can display the aorta and all its branches with high resolution and fast. It most accurately determines the assessment of the diameter of aortic aneurysms. It shows acute aortic syndromes (aortic dissection, intramural hematoma, penetrating atherosclerotic ulcer) and traumatic aortic injuries with high sensitivity and specificity (Yoshida et al., 2003). It is beneficial in identifying concomitant coronary involvement, hemopericardium, and dissection entry tears (Imoto et al., 2013). To fully define the dissection, an arterial phase-contrast CT angiography image should be obtained from the thoracic inlet to the level of the femoral artery.

B) MRI: It covers all the aorta and its branches. Inflammation may characterize acute aortic syndromes and aortic wall changes. Ionizing radiation is not used and usually is shot without contrast material (Barra, Kanji, Malette, & Pagnoux, 2018). Therefore, MRI is the first choice for evaluating congenital aortic abnormalities. It is suitable for serial imaging in young patients (Potthast et al., 2010). However, its use in aortic imaging is limited because it is not ideal for patients with permanent metallic material, has a long acquisition time, and is not as common as CT (Krishnam et al., 2010; Moore et al., 2002; Potthast et al., 2010).

C) TTE: It is the first method used for non-emergency imaging of the thoracic aorta. Although not ideal for imaging the arcus aorta, it is useful for imaging the aortic root and ascending aorta. It can be helpful in the diagnosis of aortic coarctation and patent ductus arteriosus (PDA). It may help detect complications such as aortic valve regurgitation, left ventricular dysfunction, and cardiac tamponade (Evangelista et al., 2010; Goldstein et al., 2015).

D) TEE: Acquires high-resolution images of most of the thoracic aorta except for a short segment of the distal ascending aorta just proximal to the innominate artery. It is beneficial in detailing the anatomy and function of the aortic valve. However, the need for an experienced observer causes it to remain in the background in the first diagnosis. It is beneficial in intraoperative evaluation (Evangelista et al., 2010; Goldstein et al., 2015).

E) Abdominal US: It is the recommended diagnostic tool, especially for screening and monitoring of abdominal aortic aneurysm (AAA) (Harter, Gross, Callen, & Barth, 1982; Owens et al., 2019; Steiner, Rubens, Weiss, Lerner, & Asztely, 1986). The aortic diameter >3 cm measured from the outer edge to the outer edge in an anteroposterior or transverse view is a warning (Ellis, Powell, & Greenhalgh, 1991; Hirsch et al., 2006). Its sensitivity approaches 100% when detecting the presence of an aneurysm (Wilmink, Forshaw, Quick, Hubbard, & Day, 2002). It is advantageous to be repeatable and not contain radiation. However, interobserver differences, obesity, and difficulty in assessing intestinal gas are limitations of ultrasonographic imaging (Long, Rouet, Lindholt, & Allaire, 2012).

Aneurysm Types and Etiologies

1) Etiology of Thoracic Aortic Aneurysm (TAA)

Treatment varies according to the cause and location of TAA. The size of the thoracic aorta differs according to age, gender, and height (Biaggi et al., 2009). Aortic root, ascending aorta, and associated aneurysms are the most common (60%), followed by descending aorta (30%) and arcus aortic aneurysms (10%). Risk factors are hypertension, smoking, hypercholesterolemia, and genetics (Obel et al., 2021). Aortic root and ascending thoracic aortic aneurysms correlate more with genetics and manifestation at a young age, while descending thoracic aortic aneurysms tend to occur more in degenerative and elderly patients (Vapnik et al., 2016). Marfan, Ehlers Danlos, Loeys-Dietz Syndrome, gene mutations such as MYH11,

PRKG1, MYLK, bicuspid aortic valve, Turner Syndrome, aortic coarctation, congenital heart diseases (tetralogy of Fallot, transposition of great vessels, truncus arteriosus), hypertension, history of aortic dissection, giant cell arteritis, Takayasu, Behçet's disease, thoracic aortic aneurysm are etiological factors that should be considered (Pinard, Jones, & Milewicz, 2019).

2) Etiology of Abdominal Aortic Aneurysm (AAA)

Smoking history, old age, male gender, family history of FMF, atherosclerotic cardiovascular disease history, hypertension, hyperlipidemia are the most critical risk factors (Altobelli, Rapacchietta, Profeta, & Fagnano, 2018; Kent et al., 2010; Kuivaniemi et al., 2003; Larsson, Granath, Swedenborg, & Hultgren, 2009; Sakalihasan et al., 2014; Tang et al., 2016). Although AAA shares common risk factors with atherosclerosis, it is histopathologically different. It is characterized by medial degeneration of the aortic wall (Davies, 1998). Most AAAs develop intraluminal thrombi, contributing to continued wall disruption through oxidative stress, smooth muscle cell apoptosis, and adventitial inflammation (Sakalihasan et al., 2018). The complex interplay of genetic and environmental risk factors contribute to FMF, particularly advanced age, male gender, smoking, and positive family history. Patients with FMF have a family history of 10-25% (Sakalihasan et al., 2014).

Following of TAA and AAA

When TAA or AAA is detected in patients, it should be followed up at regular intervals. Considering factors such as size, age, and cause of aneurysm, early medical treatment, and surgical or endovascular repair should be considered if necessary.

TTE is a good option in patients with thoracic aortic dilatation (TAD) not at the surgical threshold. It provides clear images of the aortic root and ascending aorta and is reproducible. TEE is an excellent alternative to evaluate aortic valve anatomy and aortic dimensions in patients whose use does not provide clear images (Loren F Hiratzka et al., 2010). Cross-sectional imaging with CT is the gold standard method. Surveillance imaging frequency should be adjusted individually, and conditions such as the cause of aneurysm, aortic diameter, rate of past aortic enlargement, the proximity of diameter to the surgical threshold, and patient age should be considered. Since the rate of aortic enlargement due to non-genetic and syndromic reasons is relatively slow, the observation interval can be extended.

Abdominal USG has become the standard for AAA imaging and is widely used. CT is mainly used in preoperative planning because it provides the best visualization of the aorta and its branches. MRI is an alternative to CT. Scan every three years when AAA is 3-3.9 cm, imaging every three years when 4-4.9 cm (male), 4-4.4 cm (female) annually, and every six months when ≥5 cm (male), ≥4.5 cm (female).

Keeping Blood Pressure Under Control

Blood pressure control in TAA aims to slow its expansion, reduce possible compression on the aortic wall, prevent aortic dissection, and reduce non-aortic cardiovascular events such as myocardial infarction (MI) and stroke. Uncontrolled hypertension increases the risk of aortic dissection. For this reason, a blood pressure target of <130/80 should be achieved using antihypertensives in people with TAA (Ladouceur et al., 2007). Angiotensin receptor blocker (ARB)-beta blocker combination should be considered in the choice of antihypertensive as it causes slow enlargement of the aorta (Hofmann Bowman, Eagle, & Milewicz, 2019).

The main goal of antihypertensive therapy in AAA is to reduce cardiovascular events such as myocardial infarction and stroke and to prevent aneurysm enlargement and rupture. Uncontrolled hypertension is a well-known risk factor for aortic rupture and dissection. Thus,

achieving a blood pressure target of <130/80 reduces adverse clinical outcomes (Lewington, Clarke, Qizilbash, Peto, & Collins, 2002).

As a result, patients must keep blood pressure under control as <130/80, regardless of TAA or AAA.

Surgical Management of Aortic Aneurysms

It is usually asymptomatic, so surgery and endovascular intervention aim to reduce the risk of death by preventing conditions such as aortic dissection and rupture (M. J. Thubrikar, 1999).

Elective surgery for aortic root and ascending aortic aneurysms should be considered when the risk of rupture outweighs the risks of surgery (M. J. Thubrikar, 1999).

As large aneurysms expand, they can cause symptoms such as chest and back pain. In addition, pain may be an indication that the aorta is overgrowing. Consequently, the appearance of these symptoms indicates an increased risk of aneurysm rupture, and surgery becomes indicated (Howard et al., 2013).

Maximum aortic diameter >5.5 cm is the primary criterion for elective surgery to the aortic root and ascending TAA (Borger et al., 2018; Svensson et al., 2013). In addition, ≥0.5 cm of growth per year confirmed by CT or MRI is another indication for surgery (Borger et al., 2018; Svensson et al., 2013). According to a study, 4-4.4 cm diameter increases the risk of dissection 89 times, while ≥4.5 cm diameter increases it 348 times (Paruchuri et al., 2015).

Comparison of open surgery and endovascular repair in thoracoabdominal aneurysm (TAAA)

There is no randomized controlled trial comparing the early or late outcome of open surgery and endovascular repair for TAAA. Open surgical repair remains the treatment of choice.

Aortic dissection

Patients usually present with "predatory" or "sharp and piercing" pain in the chest, back, and sometimes in the abdomen, as described in the books. They may also present with other signs and symptoms depending on the level of involvement: >20 mmHg blood pressure difference between the extremities, dysphagia, dyspnea, hemoptysis, hoarseness, hematuria, syncope, etc (Bossone, LaBounty, & Eagle, 2017; Bossone et al., 2013; Evangelista et al., 2018; Nienaber et al., 2004).

A plain chest X-ray is not diagnostically helpful. However, some findings may raise the suspicion of aortic dissection and suggest alternative diagnoses for present symptoms (Strayer, Shearer, & Hermann, 2012).

Signs of dissection on chest x-ray (Strayer et al., 2012)

-Mediastinal enlargement

- Disruption of the prominent contour of the aortic knob

- "Calcium sign," which occurs as a separation of intimal calcification from the aortic wall by >5 mm

-Dual-density view inside the aorta

-Right trachea deviation

-Deviation of the nasogastric tube to the right

CT, MRI, and TEE accurately diagnose dissection (Shiga, Wajima, Apfel, Inoue, & Ohe, 2006). Acute aortic dissection risk scoring systems (aortic dissection detection risk score [AAD-RS] (L. F. Hiratzka et al., 2010; Nazerian et al., 2018) (Table-1), aortic simplified risk score [AORTA] (Ohle, Anjum, Bleeker, & McIsaac, 2019) (Table-2), may be stimulating in the diagnostic evaluation of patients.

Table -1. AAD-RS *(L. F. Hiratzka et al., 2010; Nazerian et al., 2018)*

High-risk conditions	**High-risk pain characteristics**	**High-risk examination findings**
Marfan or other connective tissue diseases	Sudden onset	Pulse deficit or blood pressure difference
Family history of aortic disease	Severe intensity	Focal neurological deficit
Known aortic valve disease	Predatory	Aortic regurgitation murmur
Recent aortic manipulation		Hypotension or shock
Known TAA		
For each risk category, 1 point is given if there is ≥1 risk factor.	**As a result, a score between 0-3 will occur.**	**0- Low risk** **1- Moderate risk** **2-3 High risk**

Table-2. AORTA *(Ohle et al., 2019)*

Clinical features	**Points**
Hypotension/shock	2
Aneurysm	1
Heart rate deficit	1
Neurological deficit	1
Severe pain	1
Sudden onset of pain	1
Total score ≥2 high probability	**0 -1 low probability**

Although CT, MRI, and TEE have high sensitivity and specificity, CT has become the preferred modality due to its easy access, objective results, and rapid implementation. It has been the first diagnostic method that comes to mind because it can clearly show the diagnosis and the entire scope, vascular involvement, and dissection starting point. Detecting pericardial effusion, hemopericardium, hematoma, and pleural effusion provides clinically important information to the surgeon before the surgery of the patients (Shiga et al., 2006).

TEE is a good alternative for patients with contrast material allergies or who do not have enough time to go to the CT scan room. It is non-invasive and can be applied at the bedside with an experienced user; it can show complications such as pericardial effusion and tamponade (Evangelista et al., 2010; Goldstein et al., 2015).

Medical management of aortic dissection

They need to be treated immediately. Emergency surgery (patients with type A dissection), endovascular intervention (patients with type B dissection), or both should be considered. Pain management is also crucial, along with pulse and blood pressure control. The

patient's pain can increase the degree of dissection by making it difficult to control blood pressure (Fattori et al., 2013; Jonker et al., 2012; N. Lu et al., 2019; Qin et al., 2016; Wang et al., 2020). Studies have shown that medical treatment is essential in reducing long-term side effects and surgical and endovascular repair. Beta-blockers and intravenous vasodilators are preferred for primary treatment in emergency departments to reduce heart rate and blood pressure. Oral treatment with beta-blockers, angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors has also improved long-term outcomes after discharge (Suzuki et al., 2012; Ulici et al., 2017).

Conclusion

We need to know the aorta, the largest artery in our body; any change can cause fatal complications. Anatomy of the aorta and which etiological factors are affected should be well known. Among the known diagnoses, it is one of the diseases with the mortal course and the fastest worsening of the patient's clinic. It is a preventable disease, especially by following up on symptomatic patients with risk factors, appropriate imaging methods, and arranging medical treatment. Therefore, when such patients are encountered in the emergency department or outpatient clinics, they should be addressed and followed up. Therefore, we prevent aortic dissection, which is more challenging to manage than other diseases, from becoming more common in emergency services.

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Brain-Computer Interfaces: Exploring the Convergence of Medicine and Technology

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- Breaking Barriers: Restoring Independence with Brain-Computer Interfaces
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I. Promising Possibilities: Benefits of Brain-Computer Interfaces for Movement Disorders and Paralysis

- Unleashing Potential: Transforming Lives through Brain-Computer Interfaces
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J. Onward to the Horizon: Envisioning the Future of Brain-Computer Interface Technology

- Charting the Course for Brain-Computer Interface Advancements
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A. Unveiling the Evolution of Brain-Computer Interfaces

Brain-Computer Interfaces (BCIs) have emerged as a groundbreaking field at the intersection of medicine and technology. These interfaces facilitate direct communication between the human brain and external devices, opening up possibilities for assisting individuals with various neurological conditions. To comprehend the present state and envision the future of BCIs, tracing their evolution and acknowledging the pioneering breakthroughs that have shaped this remarkable field is essential (Zimmermann, 2006).

Tracing the Journey of Brain-Computer Interface Technology:

The journey of Brain-Computer Interface technology can be traced back to the early experiments in the mid-20th century. Initial studies primarily focused on recording brain activity through invasive techniques, such as electrocorticography and single-neuron recordings. However, the development of non-invasive techniques, including electroencephalography (EEG) and functional magnetic resonance imaging (fMRI), opened up new avenues for BCI research (Alonso-Valerdi, Salido-Ruiz, & Ramirez-Mendoza, 2015; Gao, Wang, Chen, & Gao, 2021).

Pioneering Breakthroughs in Brain-Computer Interfaces:

Throughout the history of BCIs, several significant breakthroughs have propelled the field forward. One notable milestone was the discovery of the event-related potential (ERP) component known as the P300, which demonstrated the possibility of decoding user intentions through brain signals. This finding laid the foundation for the development of early BCI systems. Another key advancement was the successful demonstration of brain-controlled robotic devices, enabling individuals to perform complex tasks using their thoughts. These pioneering breakthroughs showcased the transformative potential of BCIs in empowering individuals with disabilities (He, Yuan, Meng, & Gao, 2020; Nijholt et al., 2008).

B: A Closer Look at the Diverse Types of Brain-Computer Interfaces

Brain-Computer Interfaces (BCIs) encompass diverse technologies that enable direct communication between the human brain and external devices. Understanding the different variants of BCIs and their applications is crucial in comprehending their breadth of possibilities in various domains, including medicine, assistive technologies, and neurorehabilitation (Ganguly et al., 2009; Waldert et al., 2009).

Decoding the Variants of Brain-Computer Interfaces:

Brain-Computer Interfaces can be categorized based on the underlying techniques and modalities used to acquire and interpret brain signals. One prominent type is the electroencephalography (EEG)-based BCI, which measures electrical brain activity through electrodes placed on the scalp. EEG-based BCIs are non-invasive, portable, and have found applications in areas such as communication, control of external devices, and neurofeedback therapy (Haar, Dinstein, Shelef, & Donchin, 2017).

Another variant is the invasive BCI, which involves implanting electrodes directly into the brain tissue to record neural signals with higher spatial resolution. Invasive BCIs offer finer control and higher information transfer rates, making them suitable for applications like neuroprosthetics and restoring motor function in individuals with paralysis (Diedrichsen, Wiestler, & Krakauer, 2013; Leeb et al., 2007).

Additionally, hybrid BCIs combine multiple modalities, such as EEG and functional near-infrared spectroscopy (fNIRS), to enhance the accuracy and reliability of signal acquisition. These hybrid systems leverage the complementary strengths of different modalities to improve overall BCI performance (Takahashi et al., 2017).

Understanding the Applications and Modalities:

The applications of BCIs span a wide spectrum, including assistive technologies for individuals with disabilities, neurorehabilitation for motor disorders, and cognitive enhancement. BCIs have shown promise in enabling communication for individuals with severe paralysis, restoring motor control in patients with spinal cord injuries, and even enhancing cognitive functions in healthy individuals (J. Wolpaw, Birbaumer, McFarland, Pfurtscheller, & Vaughan, 2002).

Modalities within BCIs can vary depending on the specific application. Motor imagery-based BCIs rely on decoding brain signals associated with imagined movements, while sensory-based BCIs tap into the brain's response to external stimuli. Cognitive-based BCIs leverage brain activity patterns related to attention, memory, and other cognitive processes to enable interaction with external devices (Pfurtscheller, Müller, Pfurtscheller, Gerner, & Rupp, 2003; Schneider, Fins, & Wolpaw, 2012).

Understanding the diverse types of BCIs and their applications is vital for harnessing their potential in addressing various challenges individuals with neurological conditions face.

C: Unraveling the Mechanisms: How Brain-Computer Interfaces Work

Brain-Computer Interfaces (BCIs) operate on intricate principles that enable the translation of neural activity into meaningful commands for external devices. Unraveling the mechanisms behind BCIs is essential for comprehending the fascinating interaction between the human brain and machines, bridging the gap between these two realms (Vaughan et al., 2003; J. R. Wolpaw et al., 2000).

Delving into the Principles of Brain-Computer Interface Technology:

BCIs rely on the fundamental principle of neuroplasticity—the brain's ability to adapt and reorganize itself based on experience and learning. By exploiting this plasticity, BCIs can

establish a communication pathway between the brain and external devices (Daly & Wolpaw, 2008).

The process of BCI operation involves multiple stages. Initially, neural signals are acquired using various techniques such as electroencephalography (EEG), electrocorticography (ECoG), or intracortical recordings. These signals are then processed to extract relevant features, such as spectral patterns or event-related potentials (Blankertz, Tomioka, Lemm, Kawanabe, & Muller, 2007; Lotte et al., 2018; Lotte, Congedo, Lécuyer, Lamarche, & Arnaldi, 2007).

Next, sophisticated algorithms and signal-processing techniques are employed to interpret the extracted features and translate them into actionable commands. Machine learning algorithms, such as support vector machines (SVMs) or artificial neural networks, are commonly employed to decode the user's intention from the recorded brain activity (Collinger et al., 2013; Lebedev & Nicolelis, 2006; Millán et al., 2010).

Finally, the decoded commands control external devices, ranging from robotic prosthetics to virtual avatars or computer interfaces. The interface between the BCI and the device can be achieved through direct electrical stimulation, electromyography (EMG), or other output modalities.

Bridging the Gap Between Brain and Machine:

The successful functioning of BCIs relies on establishing effective bidirectional communication between the brain and the external device. Feedback mechanisms play a crucial role, enabling users to perceive and interpret the output generated by the BCI. Real-time feedback provides a closed-loop system, allowing users to adapt and refine their brain signals based on the external feedback they receive (Millán et al., 2010).

To bridge the gap between brain and machine, BCIs also require calibration and training sessions to establish reliable and accurate signal decoding. Users undergo training protocols to enhance their control over the BCI and improve signal-to-command mapping.

Understanding the principles and mechanisms underlying BCIs is instrumental in advancing their development and optimizing their performance, ultimately leading to more seamless and intuitive interactions between the human brain and external technologies (Gao et al., 2021).

D. Overcoming Challenges: The Limitations of Brain-Computer Interfaces

While Brain-Computer Interfaces (BCIs) hold immense potential, they are not without limitations. Exploring the frontiers of BCI technology involves a comprehensive understanding of and actively addressing these challenges. By identifying and overcoming hurdles, researchers strive to push the boundaries of what BCIs can achieve, seeking innovative solutions to enhance their capabilities.

Exploring the Frontiers of Brain-Computer Interface Technology:

BCIs face several inherent challenges that limit their performance and widespread adoption. One primary challenge lies in the acquisition of accurate and reliable brain signals. Various factors can affect signal quality, including noise interference, signal artifacts, and variations in brain activity across individuals. Advancements in signal processing techniques, sensor technologies, and data analysis methods are continually being pursued to mitigate these challenges.

Another frontier is enhancing the adaptability and robustness of BCIs. Users' neural signals can evolve, requiring continuous calibration and adaptation to maintain optimal performance. Developing adaptive algorithms and personalized training paradigms can aid in overcoming this limitation, allowing BCIs to accommodate changes in brain activity and user needs.

Addressing Hurdles and Seeking Solutions:

The development of BCIs necessitates addressing ethical and practical considerations. Ensuring user privacy, data security, and informed consent are critical when dealing with sensitive brain-related information. Researchers and policymakers collaborate to establish guidelines and regulations to protect the rights and well-being of BCI users.

Improving the usability and user experience of BCIs is another vital aspect. Streamlining the setup and calibration processes, reducing system complexity, and providing intuitive user interfaces can enhance the acceptance and usability of BCIs for individuals with varying levels of technical expertise.

Furthermore, integrating BCIs with existing medical practices and assistive technologies requires interdisciplinary collaboration and standardization efforts. Aligning protocols, data formats, and interoperability standards among BCI systems can facilitate advancements and widespread adoption.

By actively addressing these challenges and seeking innovative solutions, researchers and engineers strive to push the frontiers of BCI technology, making BCIs more accessible, reliable, and beneficial for a broader range of applications and users.

E. Envisioning the Future: Advancements on the Horizon

The future of Brain-Computer Interfaces (BCIs) holds immense promise, with a multitude of advancements and possibilities on the horizon. By exploring futuristic prospects and emerging trends in BCI technology, we can envision a future where BCIs revolutionize healthcare, communication, neurorehabilitation, and human-machine interactions.

Futuristic Prospects and Possibilities:

BCIs have the potential to transform various domains in unprecedented ways. In healthcare, BCIs may enable novel treatments for neurological disorders by providing targeted stimulation or promoting neural plasticity. They could revolutionize communication by allowing direct brain-to-brain communication, bypassing traditional sensory channels. Moreover, BCIs might enhance human cognition and memory, opening up possibilities for cognitive augmentation and accelerated learning.

Emerging Trends in Brain-Computer Interface Technology:

Several emerging trends are shaping the future of BCI technology. One notable trend is the integration of BCIs with augmented and virtual reality (AR/VR) technologies, creating immersive experiences and enabling neurofeedback-based training and therapy. Additionally, the development of miniaturized and wireless sensors offers greater mobility and comfort for users, facilitating long-term use of BCIs in real-world settings.

Another trend is incorporating artificial intelligence (AI) and machine learning techniques into BCIs. AI algorithms can enhance signal processing, improve decoding accuracy, and enable adaptive BCI systems that adapt to users' changing brain patterns. These advances hold the potential to create more robust and personalized BCI applications (Millán et al., 2010).

Furthermore, exploring novel BCI modalities, such as optogenetics, nanotechnology, or hybrid brain-machine interfaces, presents exciting avenues for future research. These modalities aim to enhance the specificity, resolution, and biocompatibility of BCIs, further expanding their capabilities and potential applications.

By embracing these emerging trends and fostering interdisciplinary collaborations, researchers, engineers, and healthcare professionals can shape a future where BCIs transform lives, pushing the boundaries of what is currently deemed possible (Lebedev & Nicolelis, 2006).

F. Enhancing Quality of Life: Transformative Potential of Brain-Computer Interfaces

Brain-Computer Interfaces (BCIs) hold tremendous transformative potential in enhancing the quality of life for individuals with neurological conditions. By empowering individuals through BCIs and revolutionizing healthcare and assistive technologies, we can unlock new possibilities for independence, communication, and improved well-being.

Empowering Individuals through Brain-Computer Interfaces:

BCIs empower individuals by restoring or augmenting their abilities to interact with the world. For individuals with severe motor impairments, BCIs offer a means to communicate, control their environment, and regain a sense of agency. By decoding their intentions and translating them into actions, BCIs can enable individuals to type, operate robotic prosthetics, or navigate assistive technologies with their thoughts.

BCIs also have the potential to enhance cognitive abilities. Brain-computer interfaces can be utilized to create closed-loop systems that provide neurofeedback, enabling users to improve attention, memory, and cognitive processing. This cognitive enhancement can benefit individuals with attention deficits, memory impairments, or other cognitive challenges (Vaughan et al., 2003).

Revolutionizing Healthcare and Assistive Technologies:

The impact of BCIs extends beyond individual empowerment and reaches into healthcare and assistive technology domains. In healthcare, BCIs have the potential to revolutionize diagnostics and treatment by providing objective measures of brain activity and enabling personalized interventions. BCIs can assist in neurorehabilitation, facilitating recovery from motor disorders, stroke, or traumatic brain injuries by leveraging neuroplasticity and offering targeted therapy.

BCIs also play a crucial role in assistive technologies. Individuals with motor impairments can regain mobility and independence by integrating BCIs with prosthetics, exoskeletons, and other assistive devices. BCIs enable direct brain control of these devices, creating seamless interfaces between the human mind and external technologies (Gao et al., 2021).

Moreover, BCIs have the potential to enhance the lives of individuals with neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS) or spinal muscular atrophy (SMA), by enabling communication and control even in the later stages of the disease.

The transformative potential of BCIs in healthcare and assistive technologies improves the lives of individuals with neurological conditions and inspires advancements in research, policy, and accessibility, fostering a more inclusive and supportive society.

G. Empowering Movement: Brain-Computer Interfaces for Motor Disorders

Brain-Computer Interfaces (BCIs) have the potential to revolutionize the treatment of movement disorders by offering new avenues for restoring mobility and empowering individuals. Through the integration of BCIs, we can unleash the potential of these interfaces in improving the lives of individuals with motor disorders, opening doors to increased independence and mobility (Takahashi et al., 2017).

Revolutionizing the Treatment of Movement Disorders:

Movement disorders, such as paralysis, Parkinson's disease, or spinal cord injuries, impose significant limitations on individuals' ability to perform basic motor functions. BCIs offer a transformative approach to address these challenges by bypassing the impaired motor pathways and directly decoding neural signals associated with intended movements.

By leveraging BCIs, individuals with movement disorders can regain control over their environment and restore their ability to engage in daily activities. BCIs can enable them to operate assistive technologies, control robotic prosthetics, or manipulate virtual avatars using their own neural activity. This revolutionizes the treatment landscape, providing individuals with newfound independence and improving their overall quality of life (Diedrichsen et al., 2013).

Unleashing the Potential of Brain-Computer Interfaces in Restoring Mobility:

BCIs hold immense potential in restoring mobility for individuals with motor disorders. By decoding the neural signals related to movement intentions, BCIs can drive exoskeletons or orthoses, enabling individuals to regain ambulation. This breakthrough technology offers an opportunity for individuals with paralysis or gait impairments to regain the ability to walk and perform activities that were previously beyond their reach.

BCIs can also be harnessed for neurorehabilitation purposes, facilitating the recovery and relearning of motor skills. BCIs can promote neural plasticity, enhance rehabilitation outcomes, and accelerate recovery by providing real-time feedback and guiding individuals through motor tasks.

The integration of BCIs with motor disorder treatments presents a paradigm shift in addressing movement impairments. By harnessing the potential of BCIs, we can unlock new possibilities for restoring mobility, promoting independence, and enhancing the overall well-being of individuals with motor disorders (Haar et al., 2017).

H. Beyond Boundaries: Brain-Computer Interfaces for Paralysis

Brain-Computer Interfaces (BCIs) offer remarkable possibilities for individuals with paralysis, breaking barriers and redefining their ability to communicate, control their environment, and regain independence. By harnessing the power of BCIs, we can empower individuals with paralysis to overcome physical limitations and enhance their quality of life (Haar et al., 2017).

Breaking Barriers: Restoring Independence with Brain-Computer Interfaces:

Paralysis, whether caused by spinal cord injuries, neurological conditions, or other factors, severely limits an individual's ability to move and interact with the world. BCIs provide a pathway for restoring independence by bypassing the impaired motor pathways and enabling direct communication between the brain and external devices.

With BCIs, individuals with paralysis can regain control over their environment and perform actions previously out of reach. They can type messages, control robotic limbs,

manipulate virtual objects, or navigate assistive technologies using their neural signals. These interfaces empower individuals, allowing them to engage in daily activities, connect with others, and regain a sense of agency and autonomy (He et al., 2020).

Redefining Communication and Control for Individuals with Paralysis:

BCIs redefine communication and control for individuals with paralysis, opening up new avenues for self-expression and interaction. Through the decoding of brain signals, BCIs enable individuals to communicate through speech synthesis, text-based communication, or even direct brain-to-brain communication. These interfaces provide a lifeline for individuals who are unable to speak or use traditional means of communication.

Moreover, BCIs expand the possibilities of control beyond physical limitations. Individuals with paralysis can operate devices, control their environment, and engage in leisure activities using their thoughts alone. This redefines the boundaries of control and offers a new level of independence for individuals with paralysis.

By embracing the potential of BCIs, we can transform the lives of individuals with paralysis, enabling them to break free from physical constraints, communicate with the world, and redefine their sense of self (Collinger et al., 2013).

I. Promising Possibilities: Benefits of Brain-Computer Interfaces for Movement Disorders and Paralysis

Brain-Computer Interfaces (BCIs) offer promising possibilities and transformative benefits for individuals with movement disorders and paralysis. By harnessing the potential of BCIs, we can unleash a new era of improved quality of life, independence, and well-being for those facing these challenges.

Unleashing Potential: Transforming Lives through Brain-Computer Interfaces:

BCIs hold the key to transforming lives by enabling individuals with movement disorders and paralysis to regain control over their bodies and environment. These interfaces provide a direct communication pathway between the brain and external devices, circumventing the limitations imposed by impaired motor functions.

Through BCIs, individuals can regain the ability to perform essential motor functions, such as grasping objects, walking, or speaking. They can control assistive technologies, prosthetic limbs, or robotic devices with their thoughts, enabling them to navigate the world with newfound independence and agency.

Illuminating the Path to Improved Quality of Life:

The benefits of BCIs extend beyond regaining motor control. BCIs can potentially enhance the overall quality of life for individuals with movement disorders and paralysis. By restoring or augmenting communication abilities, BCIs provide a means for individuals to express themselves, connect with others, and actively participate in social interactions.

Furthermore, BCIs can contribute to neurorehabilitation efforts, promoting recovery, and facilitating motor skill relearning. The ability to provide real-time feedback and personalized training through BCIs enhances rehabilitation outcomes, accelerates the recovery process, and improves functional outcomes.

The possibilities offered by BCIs illuminate a path to improved quality of life, fostering a sense of empowerment, dignity, and well-being for individuals facing movement disorders and paralysis (Gao et al., 2021; Lebedev & Nicolelis, 2006; Lotte et al., 2018).

G. Onward to the Horizon: Envisioning the Future of Brain-Computer Interface Technology

The future of Brain-Computer Interface (BCI) technology is a horizon brimming with possibilities and uncharted waters. By charting the course for advancements in BCIs, we can navigate towards a future where these interfaces reach new levels of sophistication, integration, and transformative impact.

Charting the Course for Brain-Computer Interface Advancements:

Advancements in BCIs will be driven by a multidimensional approach, encompassing technological innovations, scientific discoveries, and interdisciplinary collaborations. Refining signal acquisition techniques like high-density electroencephalography (EEG) arrays and novel implantable sensors will enhance recorded brain activity's spatial and temporal resolution. Additionally, advancements in machine learning algorithms, deep neural networks, and artificial intelligence will enable more accurate and robust decoding of complex brain signals (Blankertz et al., 2007; Lotte et al., 2018).

Integration is another crucial aspect. BCIs will converge with other cutting-edge technologies, such as augmented and virtual reality (AR/VR), internet of things (IoT), and wearable devices, creating synergistic systems with seamless human-machine integration. These integrations will enhance user experience, expand application domains, and enable more natural and intuitive interaction between individuals and their environment.

Navigating the Uncharted Waters of Tomorrow's Technology:

The future of BCIs will witness the emergence of novel modalities and applications. Optogenetics, nanotechnology, and hybrid brain-machine interfaces will unlock new frontiers in BCI research, offering enhanced spatial resolution, biocompatibility, and specificity. These advancements will enable precise control and modulation of neural activity, paving the way for groundbreaking therapeutic interventions and neuroprosthetics.

BCIs will extend beyond medical and assistive domains, finding applications in areas such as gaming, entertainment, and cognitive enhancement. BCIs will redefine the boundaries of human-machine interactions, allowing individuals to seamlessly interface with virtual environments, control avatars with their thoughts, and unlock new realms of cognitive potential.

Moreover, ethical, legal, and societal considerations will shape the future of BCIs. Regulations and guidelines will be developed to ensure privacy, informed consent, and equitable access. Interdisciplinary dialogues and collaborations among researchers, clinicians, policymakers, and ethicists will be vital to navigate these uncharted waters and address the multifaceted implications of BCI technology.

As we sail towards the future, envisioning the horizon of BCIs, we must embrace an agile and forward-thinking mindset, fueled by curiosity, collaboration, and a shared vision to harness the transformative potential of this remarkable technology (Gao et al., 2021; Lebedev & Nicolelis, 2006; Lotte et al., 2018).

To Summarize:

In this chapter, we have delved into the fascinating world of Brain-Computer Interfaces (BCIs) and explored their convergence with medicine and technology. We began by tracing the evolution of BCIs, from their early beginnings to the pioneering breakthroughs that have shaped

their development. We then examined the diverse types of BCIs, including electroencephalography (EEG)-based, invasive, and hybrid interfaces, and explored their applications and modalities in various domains.

Next, we unraveled the mechanisms behind BCIs, understanding the principles that allow these interfaces to translate neural activity into actionable commands. We discussed bridging the gap between the brain and machines, highlighting the importance of calibration, training, and feedback mechanisms in optimizing BCI performance.

We also acknowledged the challenges and limitations that BCIs face. From signal acquisition to adaptability and usability, we explored the ongoing efforts to address these hurdles and find innovative solutions. Additionally, ethical, and practical considerations were highlighted, emphasizing the need for privacy, security, and standardization in BCI technology.

Throughout the chapter, we emphasized the transformative potential of BCIs. We discussed how BCIs can empower individuals with movement disorders and paralysis, revolutionizing their treatment and offering new possibilities for restoring mobility and independence. We also explored the benefits of BCIs in enhancing quality of life, communication, and control for individuals facing neurological conditions.

Looking towards the future, we envisioned the horizon of BCI technology. We discussed the promising possibilities of advancements, including the integration of BCIs with augmented reality, artificial intelligence, and emerging modalities. We emphasized the importance of charting the course for BCI advancements and navigating the uncharted waters, considering this transformative technology's ethical, legal, and societal implications.

In conclusion, BCIs hold immense promise in revolutionizing healthcare, assistive technologies, and human-machine interactions. With ongoing research, collaboration, and innovation, we can unleash the full potential of BCIs, transforming lives and opening doors to a future where the boundaries between the human brain and technology blur, creating a world of enhanced communication, mobility, and quality of life.

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Pyogenic Spondylodiscitis

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Introduction

Pyogenic spondylodiscitis, also known as infectious spondylodiscitis, is a rare but potentially debilitating condition involving infection and inflammation of the intervertebral discs and adjacent vertebral bodies (Gouliouris et al., 2010). This spinal infection is primarily caused by bacteria, with Staphylococcus aureus being the most common pathogen (Rutges et al., 2015). Pyogenic spondylodiscitis can occur at any age and affect any part of the spine, but it most commonly affects the lumbar spine (Berbari et al., 2015). Symptoms of pyogenic spondylodiscitis include severe back pain, fever, muscle spasms, and neurological deficits (Zimmerli, 2010). Early diagnosis and appropriate treatment are essential to prevent serious complications such as spinal instability, deformity, or paralysis (Kehrer et al., 2014).

Although pyogenic spondylodiscitis is rare, its incidence has steadily increased in recent years, mainly due to an aging population, a higher prevalence of chronic diseases, and increased use of invasive spinal procedures (Akiyama et al., 2013). The incidence of pyogenic spondylodiscitis is estimated to be 2.4-7.5 cases per 100,000 people per year, with higher rates reported in immunocompromised individuals and those with underlying medical conditions (Trecarichi et al., 2012). Pyogenic spondylodiscitis significantly impacts both patients and healthcare systems, often leading to prolonged hospital stays, the need for surgical intervention, and long-term disability (Alton et al., 2015).

The study's primary objective is to comprehensively review the current literature on pyogenic spondylodiscitis, focusing on its epidemiology, pathophysiology, clinical presentation, diagnostic modalities, and treatment options (Issa et al., 2018). This study aims to identify the risk factors associated with pyogenic spondylodiscitis and to discuss the challenges in its early diagnosis and management (Torda et al., 1995). By synthesizing the existing knowledge on this topic, we hope to contribute to developing evidence-based guidelines for preventing, diagnosing, and treating pyogenic spondylodiscitis, ultimately improving patient outcomes and reducing the burden on healthcare systems (Cottle & Riordan, 2008).

Etiology and Pathogenesis

Pyogenic spondylodiscitis results from the hematogenous spread of bacteria from a primary site of infection or by direct inoculation during spinal surgery or invasive procedures (Nickerson & Sinha, 2016). Common primary sources of infection include the skin, soft tissues, respiratory tract, genitourinary tract, and gastrointestinal tract (Mylona et al., 2009). In some cases, the primary source of infection may not be identified. Risk factors for developing pyogenic spondylodiscitis include immunosuppression, diabetes mellitus, intravenous drug use, renal insufficiency, and a history of spinal surgery or instrumentation (Marie Beronius et al., 2001).

Staphylococcus aureus is the most common pathogen in pyogenic spondylodiscitis, accounting for 40-60% of cases (McHenry et al., 2002). Other bacterial pathogens include

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Streptococcus species, Escherichia coli, and Pseudomonas aeruginosa (Grammatıco et al., 2007). Rarely, fungal and mycobacterial organisms can cause spondylodiscitis., The virulence factors of these microorganisms contribute to their ability to invade the disc and vertebral bodies, resist host immune defense and cause tissue damage (Norden & Niederriter, 1988). Among the virulence factors, bacterial adhesins, proteases, and biofilm formation play an essential role in the pathogenesis of pyogenic spondylodiscitis (Zimmerli & Sendi, 2011).

The immune system controls and eliminates infections. However, several factors contribute to the establishment and progression of infection in pyogenic spondylodiscitis. The avascular nature of the disc limits the immune response and the delivery of antibiotics, facilitating bacterial colonization (Hawley et al., 1996). In addition, the biofilms formed by bacteria further impair the immune response and antibiotic penetration, making the infection difficult to treat (Donlan & Costerton, 2002). In addition, underlying medical conditions or immunosuppressive treatments can weaken the host's immune response, increasing susceptibility to pyogenic spondylodiscitis (Nussbaum et al., 1992).

Clinical Findings and Diagnosis

The clinical presentation of pyogenic spondylodiscitis is often insidious and non-specific, making early diagnosis difficult (Carragee, 1997). Common signs and symptoms include localized back pain, tenderness, muscle spasms, and reduced spinal mobility (Govender, 2005). Systemic symptoms such as fever, chills, and malaise may also be present. In more advanced cases, neurological deficits such as motor weakness, sensory disturbances, or bowel and bladder dysfunction may occur due to compression or irritation of the spinal cord or nerve roots (Darouiche, 2006).

Blood tests are helpful in the diagnosis of pyogenic spondylodiscitis. Elevated inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are common, although they are not specific to this condition (Skaf et al., 2010). A complete blood count may show leukocytosis, suggesting systemic infection. Blood cultures should be obtained to identify the causative organism and guide antibiotic therapy. However, blood cultures are positive in only 30-60% of cases (Gemmel et al., 2010).

Conventional radiography (X-ray) is often the first imaging modality used, but it has low sensitivity, especially in the early stages of the disease (Kowalski et al., 2007). Computed tomography (CT) provides better visualization of bone destruction and can help to assess the extent of infection (Ledermann et al., 2003). However, magnetic resonance imaging (MRI) is considered the gold standard for diagnosing pyogenic spondylodiscitis, with a sensitivity and specificity of over 90% (Modic et al., 1985). MRI can detect early changes in the disc and vertebral bodies, such as edema, inflammation, and abscess formation, and can also help assess the involvement of adjacent soft tissues and the spinal canal (Stäbler & Reiser, 2001).

Percutaneous CT- or fluoroscopy-guided biopsy of the affected disc or vertebral body is essential for definitive diagnosis and identification of the causative organism (Zarghooni et al., 2011). Biopsy samples should be sent for culture and susceptibility testing, histopathological examination, and molecular testing, such as polymerase chain reaction (PCR). The results of these analyses will guide the selection of appropriate antimicrobial therapy and help to monitor the response to treatment (Zimmerli, 2010).

Risk Factors

Age is an important demographic risk factor for pyogenic spondylodiscitis, with a higher incidence observed in older adults (Berbari et al., 2015). The increased susceptibility may be due to age-related degenerative changes in the spine, decreased immune function, and a higher

prevalence of comorbidities. The male gender has also been associated with a higher risk of developing pyogenic spondylodiscitis, possibly due to differences in occupational exposure, hormonal influences, or other lifestyle factors (Kehrer et al., 2014).

Due to primary immune disorders or secondary causes such as chemotherapy, organ transplantation, or immunosuppressive drugs, immunodeficiency increases the risk of pyogenic spondylodiscitis (Torda et al., 1995). Systemic diseases such as diabetes mellitus, chronic kidney disease, malignancies, and cirrhosis may also predispose individuals to spondylodiscitis by compromising immune function and increasing susceptibility to infection (Trecarichi et al., 2012).

Invasive spinal procedures, such as spinal surgery, epidural injections, or diagnostic lumbar punctures, can introduce infectious agents directly into the spinal structures, leading to pyogenic spondylodiscitis (Akiyama et al., 2013). Spinal implants or hardware, such as pedicle screws and rods, may further increase the risk of infection due to biofilm formation on foreign materials (Sendi & Zimmerli, 2011).

Other risk factors for developing pyogenic spondylodiscitis include intravenous drug use, which can introduce infectious agents into the bloodstream, and pre-existing spinal conditions such as degenerative disc disease or trauma, which can compromise spinal blood flow and predispose to infection (Butler et al., 2006, Marie Beronius et al., 2001). In addition, obesity, smoking, and malnutrition can impair immune function and increase susceptibility to infection, including spondylodiscitis (Gouliouris et al., 2010).

Treatment Approaches

The initial approach to treating pyogenic spondylodiscitis often involves conservative management, including antibiotics, analgesics, and immobilization (Zimmerli, 2010). Clinicians should initiate antibiotic therapy only after identifying the causative organism unless clinical circumstances like severe neutropenia or sepsis are present (Ozuna & Delamarter, 1996). Based on the clinician's best judgment of the likely causative organism(s) (Ozuna & Delamarter, 1996) and the patient's risk factors (Table 1), patients should receive empiric broad-spectrum antibiotics. After identifying the organism, clinicians should administer targeted intravenous antibiotics.

Table 1 *Likely offending organisms in pyogenic spontaneous spondylodiscitis, based on the patient's clinical history or physical findings*

Infection	**Bacteria**
Skin infection	Staphylococcus aureus
IVDA	Pseudomonas aeruginosa
Genitourinary tract infection	Escherichia coli/Proteus spp.
Respiratory tract infection	Streptococcus pneumoniae
Alcoholism	Klebsiella pneumoniae
Acute endocarditis	Staphylococcus aureus
Subacute endocarditis	Streptococcus spp.

Also the ability of bone and disc penetration should be considered. Bone penetration of many antibiotics has been tested in vivo and in vitro, but because of the lack of standardized

methodology, results are not always comparable (Cunha et al., 1977, Summersgill et al., 1982, Landersdorfer et al., 2009)

With the available data we know that clindamycin, fluoroquinolones, macrolides, rifampicin, fusidic acid, metronidazole, and linezolid reach good levels in bone tissue. Beta-lactam antibiotics and glycopeptides achieve moderate levels, and aminoglycosides diffuse poorly into the bone (Grados et al., 2007).

Due to the relatively low vascularity in necrotic bone, areas of poor penetration and low oxygen tension result at the site of infection; this can compromise the activity of certain antimicrobials such as gentamicin and vancomycin (Norden & Shaffer, 1983,4 Weinstein, 1976).

Rifampin has a good tissue penetration index and is probably active on biofilm phenotypes. However, it should never be given as monotherapy, due to the rapid development of resistance. Regimens including rifampin combined with other antimicrobials are widely used in bone and joint infections; however, very few compelling data support this strategy. In fact, the available data indicate that rifampin combination therapy is clinically effective in biofilm infections and in the presence of prosthetic implants (Forrest & Tamura, 2010). No controlled trials are available to de- fine weather combination therapy with rifampin is beneficial for treating PS.

Table 2 summarizes the suggested antibiotic regimens for the i.v. treatment of pyogenic spondylodiscitis. Suggestions are based on guidelines and a review of observational studies (Liu et al., 2011, Skaf et al., 2010).

Table 2. *Suggested antibiotic regimens for the i.v. treatment of PS*

Methicillin-sensitive Staphylococcus aureus	Flucloxacillin 2 g q6h iv or equivalent anti-staphylococcal penicillin OR Ceftriaxone 2 g daily
Methicillin-resistant Staphylococcus aureus	Vancomycin 15-20 mg/kg q12h-q8h iv aiming for pre-dose levels of 15-20 mg/L OR Teicoplanin 8-12 mg/kg daily iv after loading OR Daptomycin 6 mg/kg/day IV QD 6-10 mg/kg/day IV QD
Enterobacteriaceae	Ciprofloxacin 400 mg q12h iv or 750 mg q12h orally OR Ceftriaxone 2 g daily iv OR Meropenem 1 g q8h iv
Pseudomonas aeruginos	Ceftazidime 2 g q8h iv+aminoglycosides OR Meropenem 1 g q8h iv+aminoglycosides OR Ciprofloxacin 400 mg q12h iv or 750 mg q12h orally OR combination of two different antibiotic classes
Streptococci	Benzylpenicillin 2.4 g q6h iv OR Ceftriaxone 2 g once daily iv
Enterococcus faecalis	Amoxicillin 2 g q6h iv + gentamicin 1 mg/kg q12h-q8h iv
Enterococcus faecium	Vancomycin 15 mg/kg q12h iv +gentamicin 1 mg/kg q12h-q8h iv
Anaerobes	Metronidazole 500 mg q8h iv OR Clindamycin 600 mg q6h i.v.

Beta-lactams have moderate bone penetration. Nonetheless, the good tolerance and the high dosages achievable parenterally make them the first choice for the induction treatment of PS caused by sensitive pathogens.

Clindamycin is a bacteriostatic antibiotic with the major advantage of higher bone penetration than beta-lactams, in the presence of relatively low serum concentrations. Because of its good bioavailability and high levels of bone, clyndamycin is a convenient choice for oral switch therapy in patients who can be discharged (Darley, 2004).

Quinolones are widely used to treat bone infections because they are active against a broad spectrum of bacteria (including adherent bacteria), penetrate macrophages and PMNCs, and reach effective bone concentration with oral administration (Hooper & Wolfson, 1991, Desplaces & Acar, 1988, Metallidis et al., 2007). Quinolones can be also used for long periods since they have a favorable safety profile. However, it should be considered that long antibiotic treatments are a well-established risk factor for the development of resistant bacterial strains (Tacconelli, 2009).

Rifampicin is peculiarly effective against bacterial biofilm and can kill phagocytosed bacteria penetrating white blood cells; it has also good bone penetration (Zimmerli, 1998). Rifampicin should never be used in monotherapy because of the rapid development of resistance, but it can be used in combination therapy with beta-lactams, with quinolones, and with vancomycin, teicoplanin or minocycline for MRSA (Clumeck et al., 1984, Yzerman, 1998). The commonest side effect is hepatic damage, so monitoring of liver function is recommended (Darley, 2004).

Fusidic acid has good bone penetration and bactericidal activity against S. aureus but, like rifampicin, it causes the rapid development of resistance, so it should be used in combination therapy (Chater, 1963, Mantero et al., 2011).

Glycopeptides are the first choice in infections caused by MRSA (Darley, 2004). Using vancomycin allows a more rapid killing of staphylococci than teicoplanin but decreases activity in anaerobic conditions (Bailey et al., 1991). Vancomycin is more nephrotoxic but more easily measurable in serum than teicoplanin (Wood, 1996, Lemaire et al., 2011, Legout et al., 2010). Teicoplanin is more frequently associated with thrombocytopenia and neutropenia (Wilson et al., 1986). Vancomycin cannot be administered once daily, whereas teicoplanin can be used for outpatient parental therapy (Graninger et al., 1995, Le Vavasseur & Zeller, 2022, Greenberg, 1990).

Daptomycin is a new lipopeptide antibiotic, active on Gram-positive bacteria, useful in the treatment of MRSA osteomyelitis, even if it is FDA-approved only for adults with S. aureus bacteremia, right-sided infective endocarditis, and skin and soft tissues infections (Liu et al., 2011). It has a rapid bactericidal activity, and there might be a possible cross-resistance with vancomycin (Boucher & Sakoulas, 2007). An interesting feature of daptomycin is its possible activity on biofilm infections (Leite et al., 2011). The main adverse effects are elevation in creatinine phosphokinase (which appeared in patients treated with the maximal doses), weakness, myalgia, and renal failure; eosinophilic pneumonia is rare (Miller et al., 2010). Further studies on its bone penetration, safety in long-term treatments, and effectiveness compared with glycopeptides are needed.

Trimethorim/sulfamethoxazole administered orally in high doses can be an alternative for treating MRSA infections. However, it is associated with adverse effects (hematologic and renal toxicity) that may limit its use in prolonged treatments (Stein et al., 1998).

Oral minocycline (with or without rifampicin) effectively treats MRSA bone infection (Qadri et al., 1994, Yuk et al., 1991). It has good bioavailability and is frequently used when shifting from parenteral to oral therapy.

Quinupristin/dalfopristin is a parenteral antibiotic with bactericidal activity against Enterococcus (E.) faecium, including VRE and S. aureus, including MRSA, it has no activity against E. faecalis (Summers et al., 2001, Reyzelman et al., 1997, Allington, 2001). Quinupristin/dalfopristin administered three times daily by central infusion can cause myalgia, which may necessitate cessation of treatment (Darley, 2004).

Linezolid is an oxazolidinone antibiotic that inhibits bacterial protein synthesis and is active against Gram-positive organisms including VRE (E. faecium and E. faecalis) and MRSA (Zurenko, 2001). There is no evidence of cross-resistance with other antibiotics. Despite its good bone penetration and complete oral bioavailability, linezolid is not approved for the treatment of osteomyelitis (Stolle et al., 2008). The use of linezolid is limited by its potential hematologic toxicity (anemia, thrombocytopenia), especially during long-term treatment, and by its high cost (Gould, 2011).

Roblot et al. assessed the risk of vertebral osteomyelitis recurrence. They found no increased risk in patients treated with antibiotics for six weeks compared with those treated for longer than six weeks. Their results suggest that reducing antibiotic therapy for spondyloarthritis to six weeks does not increase the risk of recurrence; however, the patient follow-up time was only six months after treatment (Roblot et al., 2007). The optimal total duration of antibiotic therapy remains uncertain. Observational studies have shown that treatment duration of fewer than four weeks or eight weeks results in significantly higher relapse rates compared to treatments more extended than 12 weeks (> 14%, 10%, and > 15% vs. 3.9%) (Jensen et al., 1998). Diagnosing pyogenic discitis and vertebral osteomyelitis often takes 6 to 7 weeks after symptom onset. Grados et al. recommend administering antibiotics for at least 12 weeks for chronic bone infections (Roblot et al., 2007).

Analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, may be used to manage pain and inflammation. Immobilization with a brace or external orthosis can provide additional support and help reduce pain during healing (Jensen et al., 1998).

Surgical intervention may be necessary for severe infection, neurological compromise, spinal instability, or failure of conservative treatment (Kowalski et al., 2006). Surgical options include debridement of the infected tissue, stabilization of the affected spinal segments, and intervertebral disc and spinal fusion (Kim et al., 2014). Debridement involves the removal of infected and necrotic tissue, which can help reduce bacterial load and promote healing. Stabilization can be achieved using spinal instrumentation, such as pedicle screws and rods, to support and maintain spinal alignment during healing. Intervertebral disc and spinal fusion may be performed to restore the structural integrity of the affected spinal segments (Curry et al., 2005).

Close monitoring of the patient's clinical, laboratory, and radiological findings are essential to assess the response to therapy and identify any complications (Gouliouris et al., 2010). This may involve regular clinical evaluations, serial measurements of inflammatory markers (e.g., CRP and ESR), and periodic imaging studies, such as MRI or CT scans, to monitor the resolution of infection and spinal stability (Carragee, 1997). C-reactive protein (CRP) levels are a reliable indicator of treatment success. We administer parenteral antibiotics for six weeks (or more) and oral antibiotics for 4-8 weeks, depending on the patient's response. We can send the patient home on intravenous antibiotics if the patient is stable. When switching to oral therapy, we use high doses of antimicrobial agents to ensure adequate bone concentrations. We choose antibiotics based on their high bioavailability. Properly managing

associated medical problems, such as diabetes, renal failure, and poor nutritional status, is crucial for successful clinical outcomes. Patients should be followed up for an extended period after completion of treatment to ensure complete resolution of the infection and to detect any potential relapse or complications (Roblot et al., 2007).

Treatment success is generally defined as the resolution of clinical signs and symptoms, normalization of inflammatory markers, and radiological evidence of infection resolution and spinal stability (McHenry et al., 2002). The absence of complications, such as neurological deficits, spinal deformity, or recurrent infection, indicates successful treatment (Torda et al., 1995).

Complications and Prognosis

Intra-abdominal complications of pyogenic spondylodiscitis may include abscess formation in adjacent organs, such as the psoas muscle or epidural space, and the spread of infection to other structures (Zimmerli, 2010). Spinal complications may include the development of spinal deformities, such as kyphosis, due to the destruction of vertebral bodies, intervertebral discs, and other supporting structures (Kim et al., 2014). In addition, spinal instability may occur, leading to further pain and functional impairment (Herren et al., 2017).

Neurological complications may result from direct compression of neural structures or the development of an epidural abscess, which may lead to radiculopathy, myelopathy, or cauda equina syndrome (Akcam et al., 2011). These complications can lead to significant morbidity, including chronic pain, motor and sensory deficits, and bowel or bladder dysfunction (Erşahin, 2001).

Systemic complications of pyogenic spondylodiscitis may include sepsis, disseminated intravascular coagulation, and multiple organ failure, especially if the infection is not adequately treated or controlled (Levy et al., 2018). In addition, underlying comorbidities such as diabetes mellitus or chronic kidney disease may increase the risk of systemic complications (Kehrer et al., 2016).

The prognosis for pyogenic spondylodiscitis varies, depending on factors such as the causative organism, the severity of the infection, the patient's underlying health, and the timeliness and appropriateness of treatment (Carragee et al., 1997). With prompt diagnosis and appropriate treatment, most patients can achieve a favorable outcome, including resolution of the infection, preservation of spinal function, and a return to the pre-infection quality of life (Gupta et al., 2014). However, patients who experience significant complications, particularly neurological complications, may have a poorer prognosis and reduced quality of life (Luzzati & Giacomazzi, 2012).

Prevention and Monitoring

Effective management of risk factors is critical in preventing pyogenic spondylodiscitis. This includes controlling chronic medical conditions such as diabetes mellitus and chronic kidney disease, which can compromise the immune system (Kehrer et al., 2015). Encouraging patients to maintain a healthy lifestyle with proper nutrition and exercise can also help support overall immune function (Mota et al., 2018). In the case of invasive procedures or surgery, strict adherence to aseptic techniques and perioperative antibiotic prophylaxis can minimize the risk of introducing infection (Bland, 2006).

Prompt recognition of the signs and symptoms of pyogenic spondylodiscitis can facilitate early diagnosis and treatment, potentially reducing the risk of complications and improving patient outcomes (Kim et al., 2014). Healthcare providers should maintain a high index of

suspicion for pyogenic spondylodiscitis in patients with persistent back pain, fever, and elevated inflammatory markers, primarily if they have known risk factors (Sobottke et al., 2009).

Regular clinical and radiological monitoring is essential to detect any recurrence or complications of pyogenic spondylodiscitis (Ishihara et al., 2016). This may include regular clinical assessments, laboratory tests to measure inflammatory markers, and imaging studies (e.g., MRI, CT, or X-ray) to assess spinal stability and resolution of infection (Kowalski et al., 2007).

Educating patients about the signs and symptoms of pyogenic spondylodiscitis and the importance of early treatment can help promote prompt medical attention and better outcomes (Lee & Minotti, 2003). In addition, informing patients about the condition's potential complications and long-term effects can help them understand the importance of adhering to prescribed treatment regimens and follow-up care (Akcam et al., 2011).

Conclusion

Pyogenic spondylodiscitis is a severe and potentially debilitating condition that can lead to significant morbidity and mortality if not diagnosed and treated promptly (Fraser & Till, 2002). It affects patients' quality of life and often requires long-term treatment and rehabilitation (Levy et al., 2018). It is also a significant burden on healthcare systems due to the costs associated with its diagnosis, treatment, and complications (File, 2013).

The current understanding of pyogenic spondylodiscitis, including its etiology, pathogenesis, clinical features, and risk factors, has significantly improved the ability to diagnose and manage the condition effectively (Gouliouris et al., 2011). Advances in diagnostic imaging, antibiotic therapy, and surgical techniques have greatly improved patient outcomes by reducing the risk of complications and improving long-term prognosis (Waisbren, 1960). However, further research and development of novel treatment strategies are essential to improve patient care and outcomes.

Future research should identify novel diagnostic and prognostic biomarkers, improve understanding of host-pathogen interactions, and develop novel therapeutic strategies for managing pyogenic spondylodiscitis (Grant, 2000). In addition, long-term follow-up studies are needed to better understand the disease’s natural history and evaluate the efficacy of different treatment approaches (Cunha, 2002). Finally, further research into the prevention and management of risk factors may help to minimize the incidence of pyogenic spondylodiscitis and improve overall patient outcomes (Turunc et al., 2007).

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Clinical use of Acute Phase Reactants

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INTRODUCTION

Liver cells play an important role in the synthesis of acute phase proteins (AFP). These proteins, whose serum concentrations increase as a result of inflammatory conditions, malignancy and trauma, especially infectious diseases, are called Acute Phase Reactants (AFR). In case of acute phase response, changes in some protein levels in the serum, fever, increased vascular permeability and some metabolic changes are observed. AFR are proteins whose serum concentrations increase or decrease in the inflammatory acute phase response. Those that show an increase in these proteins are called positive AFP, and those that show a decrease are called negative AFPs. Positive AFPs include C-reactive protein (CRP), fibrinogen, procalcitonin, haptoglobin, ceruloplasmin, ferritin, alpha-1 antitrypsin, serum amyloid A. Negative AFPs include albumin and transferrin (Ebersole & Cappelli, 2000) (Vercoutere et al., 2011) (Zhang et al., 1999).

POSITIVE ACUTE PHASE PROTEINS

C-REACTIVE PROTEIN (CRP)

CRP is given this name because it can precipitate the C-polysaccharide of Streptococcus pneumoniae. CRP is synthesized by the effect of cytokines (most importantly IL-6) secreted from the inflamed tissue. CRP increases in serum levels in cases caused by infection, inflammation, malignancy, and trauma (Gabay & Kushner 1999). CRP is mainly synthesized in the liver. Almost all of the circulating CRP is secreted from hepatocytes. The increase in CRP occurs shortly after inflammation, with the CRP level > 5 mg/L after six hours. CRP reaches its maximum in 48 hours. The half-life of CRP is about 19 hours. CRP slightly increases with age (Wene, Daum & McQuillan, 2000).

FIBRINOGEN

It is a blood protein synthesized in the liver, found in blood plasma, and plays an important role in coagulation. Fibrinogen is a large and complex fibrous glycoprotein with three pairs of polypeptide chains linked by 29 disulfide bonds. Fibrinogen is the precursor to “fibrin” that occurs in blood clotting. While coagulation occurs, fibrinogen turns into fibrin with the effect of thrombin substance and ionized calcium, forming the clot. In various diseases of the liver, the amount of fibrinogen in the blood decreases due to the disruption of synthesis events. In pregnancy, joint rheumatism and inflammatory conditions, the amount of fibrinogen in the blood increases. Fibrinogen may be unable to function in some congenital or postnatal disorders (Weisel, 2005) (Fuss, Palmaz & Sprague, 2001).

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PROCALCİTONİN (PCT)

The procalcitonin molecule is a protein consisting of 116 amino acids. PCT is a pre-hormone of the calcitonin hormone produced by parafollicular C cells in the thyroid gland and involved in calcium homeostasis in the human body. It is very common to use as an infection marker, especially when bacterial infection is suspected. PCT values increase in infections caused by bacteria, while PCT values do not increase in parasitic, fungal and viral infections (Horns, Draenert & Nistal 2021) (Velissaris et al., 2021). Sepsis is a systematic inflammatory response to the infectious agent that causes the infection. Sepsis is one of the most important causes of mortality in intensive care. There is no routine gold standard test for the diagnosis and prognosis of sepsis. CRP and PCT are two of the most used tests in the diagnosis of sepsis (Faix, 2013).

Clinical Conditions with PCT Measurement;

- To diagnose bacteremia and septicemia (sepsis) in adults and children and to determine the severity of the infection,
- Septic shock diagnosis, risk identification and monitoring,
- Diagnosis of bacterial infection in neutropenic patients,
- Understanding the state of the kidneys in children's urinary infections,
- In the follow-up of antibacterial therapy,
- In the diagnosis of systemic deconder infection in post-operative severe traumas, burns and multiple organ failure,
- In the differential diagnosis of bacterial and viral meningitis,
- In the differential diagnosis of bacterial and viral pneumonia due to the epidemic,
- To distinguish between inflammation and infection,

HAPTOGLOBIN

Haptoglobin is a protein whose biosynthesis is not only in the liver, but also in adipose tissue and lung. Haptoglobin binds hemoglobin in the plasma and transports it to the liver. The hemoglobin complex with haptoglobin is metabolized in the heptic reticuloendothelial system. For this reason, it is used in the diagnosis and follow-up of hemolytic anemia and in the differential diagnosis of anemia due to other diseases. Its level is decreased in hemolytic anemia. Low levels without hemolytic anemia indicate insufficient production due to liver disorders. However, it is not a test used in liver disease and follow-up. Haptoglobin levels are affected by excessive blood loss and renal dysfunction (Wassell, 2000). Haptoglobin, which is also an "acute phase" protein, has different function showing genetic polymorphism. Haptoglobin provides antioxidant and antimicrobial activity. Changes in haptoglobin levels measured in serum, increases in conditions such as inflammation, infection, malignancy, and decreases in hemolytic conditions are important in the evaluation of patients' condition. Haptoglobin is involved in the stimulation of angiogenesis. Haptoglobin has the feature of promoting cholesterol crystallization. Probably the most important biological function of haptoglobin is to act as a natural antagonist for receptor-ligand activation of the immune system, creating host defense responses against infection and inflammation (Dobryszycka, 1997).

CERULOPLASMIN

Ceruloplasmin is an α-2 globulin and consists of a single polypeptide chain. Its molecular weight is around 132,000 Daltons. It binds six copper atoms per molecule. Serum levels vary due to genetic polymorphism. Ceruloplasmin, which contains copper element and plays a role in iron metabolism, is synthesized in the liver as an acute phase reactant. In the presence of inflammation, an increase in serum levels is observed. An increase in serum levels of ceruloplasmin is observed in infections, inflammation, malignancy, trauma, obstruction and infections of the biliary tract. The increase is even more evident in RES diseases such as Hodgkin Lymphoma (Dowton & Colten 1988) (Cox & Roberts 2002).

FERRITIN

Ferritin is an iron-storing protein and does not play a role in iron transport. In clinics, ferritin level is used together to detect iron stores and evaluate transferrin saturation in iron deficiency anemia. In inflammatory conditions, IL-1,6 and interferon gamma (IFNγ) cause increased ferritin production from the liver and macrophages. The increase in ferritin levels is seen in a chronic inflammatory process, cell damage in infections, alcohol-related or non-alcoholic hepatosteatosis and chronic viral hepatitis. Ferritin causes activation of intracellular inflammatory pathways. Due to cell damage caused by inflammation, ferritin is released, causing an increase in serum levels (Kell & Pretorius, 2014) (Güvey et al., 2021).

ALPHA-1 ANTHRIPSYCINE (AAT)

Alpha-1 antitrypsin (AAT) is a 52 kDa glycoprotein produced in the liver. AAT is one of the acute phase proteins and is the main inhibitor of serine proteases in tissues and circulation. AAT deficiency is an inherited disorder that can cause pulmonary emphysema and liver disease. Serum levels of AAT increase in inflammation, infection and malignant conditions (Patel & Teckman, 2018) (Ehlers, 2014).

SERUM AMYLOID-A (SAA)

Serum amyloid-A (SAA) is a protein consisting of 124 a.a. synthesized in the liver in cases of inflammation. SAA is an acute phase reactant. The increase in serum levels of SAA is a clinical marker of active inflammation. It is used to distinguish between inflammatory and non-inflammatory diseases. It is also used in the evaluation of the treatment applied to the diseases and in the follow-up of the prognosis of the disease (Sack, 2020) (Carbone et al., 2021).

NEGATIVE ACUTE PHASE PROTEINS

ALBUMIN

Albumin is synthesized by the liver and has an average weight of 69 kDa. Its half-life is approximately 20 days, and it is the most abundant plasma protein in the blood. Its plasma concentration is higher than other proteins in normal healthy subjects (approximately 40 g/L). It makes up 60% of the proteins in the blood. Albumin; It has an important role in the exchange between organs and tissues through blood. It is the most important protein that regulates the oncotic pressure that allows large protein molecules in the blood plasma to pass through narrow areas such as capillaries. Albumin, which determines the density of blood, which is mostly water, creates oncotic pressure in the vessel. The most important functions of albumin; Nitric oxide (NO), fatty acids such as oleic and linoleic, thyroid and steroid hormones, drugs taken for treatment and vitamin B6, calcium, to ensure the transport of bilirubin and free fatty acids. Albumin deficiency, which is a negative acute phase reactant, can occur due to diet such as

inadequate and unbalanced nutrition, or it can be caused by many different infectious diseases, especially advanced liver disorders (Hülshoff et al., 2013) (Mayer & Schomerus, 1975) (Tan, 2019).

TRANSFERRIN

Transferrin, a negative acute phase reactant, is a glycoprotein and is synthesized in the liver. Its structure consists of a single polypeptide chain of about 700 amino acids. It is the major iron-bearing protein in plasma and carries two iron atoms per protein. Iron deficiency increases the synthesis of transferrin in the liver. It takes iron from the gut and transfers it to the bone marrow and other organs. It also transfers the iron to the places where it is needed. About 25 mg of Fe is released in the body daily. Many cell surfaces have receptors for transferrin. Since free Fe is toxic, this toxicity is prevented by binding to transferrin. In this way, Fe bound to transferrin is transported to where it is needed. Transferrin-Fe complex is taken up into cells by receptor-mediated endocytosis. The plasma transferrin concentration is about 300 mg/dl. Plasma transferrin level decreases in malnutrition, inflammatory conditions, liver diseases and malignancy (Gomme, McCann & Bertolini, 2005) (Tortorella & Karagiannis, 2014).

CONCLUSION

AFP are proteins synthesized by the liver in response to the acute phase response. They have a large number of different functions and features that are used in our time. While these proteins are insignificant in healthy individuals, serum levels increase rapidly in cases of infection and play a role as an infection marker.

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Current Debates in Huntington's Disease with Neuro-Radio-Pathologic and Neuropsychiatric Approaches

Esra DEMIR UNAL

Huntington's Disease (HD) is a progressive and fatal disease that shows autosomal dominant inheritance which caused by a CAG trinucleotide repeat expansion in the huntingtin gene (HTT), located on chromosome 4. The disease was first named by Dr. George Huntington in 1872 that first defined a family with choreiform movement disorder in the USA in 1872 (Bhattacharyya, 2016), and after that, hundreds of families of different genders were described in many parts of the world. HD is inherited in an autosomal dominant pattern that normally ranges between 10 to 34 CAG repeats. The pathological findings will most likely express if the CAG repeats lengths of 40 or more (Medina & ark., 2022). North American prevalence estimates range from 5 to 10 individuals per 100,000 of the general population. The genetic disorder is thought to be translated to roughly 30,000 offspring in America. Prevalence rates in North America, Europe, and Australia are generally similar, whereas rates in Asia are much lower, affecting less than one person in 100,000 (Warby, Visscher H & Collins, 2011). The neurodegenerative process is accompanied by a wide range of clinic spectrum that may involve different combinations of movement disorders (primarily chorea), dementia, and behavioral or psychiatric manifestations (Reddy, 2014)

Molecular genetics of Huntington's disease and HTT Gene Analysis

The HD gene is expressed in the 4p 16.3 region of the short arm of chromosome 4, consists of 67 exons and is 180 kb. The mutation that manifests the disease occurs with an increase in the number of CAG trinucleotides in exon 1 of the gene. Normally, the repetitions in this region are polymorphic, and these repetitions give clinical findings when they exceed the threshold value. Individuals with 26 or less CAG repeats show a normal phenotype, while 27-35 repeats usually do not manifest, but disease may occur in the next generation due to meitoic instability, which is known to increase more frequently in spermatogenesis than in oogenesis (The Huntington's Disease Collaborative Research Group, 1993). Paternal inheritance is blamed in juvenile cases and early-onset cases (Kremer & ark., 1995). In addition, it has been shown that CAG repeat increase is especially on the paternal side in patients with new-onset HD without a family history, and the number of repeats in these cases was found to be in the borderline or normal range (Trottier, Biancalana & Mandel, 1994). Although 35 or fewer CAG repeats are known not to manifest, Groen et al. reported two patients with a HD phenotype between 27 and 35 in a study conducted in 2009 (Chaganti & et al., 2017).

In general, it should be known that the disease manifests in cases with 40 or more CAG repeats. CAG repeat increase is inversely related to the age of onset of the disease. As the number of CAG repeats increases, the age of manifestation of the disease decreases. The age of onset did not differ significantly in homozygous cases, but it is known that these cases progress more rapidly (Gusella & et al., 1983).

After the detection of the HD relationship between chromosome 4, the diagnosis of the disease in the presymptomatic stage was made possible by various indirect methods (Gusell & et al., 1983, Hayden & et al., 1988, Skraastad & et al., 1991).

Clinical approach to Huntington's disease

Motor Symptoms

HD generally develops in adult life, with an average age of onset of 40 years, though cases of HD have been diagnosed in patients as young as 2 years old, ranging up to 87 years. From the time of disease onset, symptoms progress over 15–20 years (Lanska & et al., 1988). The age of onset of HD generally affects clinical presentation. Juvenile-onset HD is characterized by rigidity, bradykinesia, dystonia, and sometimes tremor and myoclonus tremors, and chorea is typically absent. The first presentation of Adult-onset HD may be with chorea, and dystonia and rigidity are added to this in advanced stages. An akinetic-rigid form of HD predominantly present with dystonia and partly with chorea can be seen in 10% of patients. There may also be learning difficulties and behavior disturbance whilst at school. Seizures occur in 30–50% of patients (Kremer, 2002).

Patients who are carriers of HD gene mutations and do not yet show symptoms in clinical motor domains are defined as pre-manifest. (Ross, Aylward & Wild, 1996). In current studies, a new term is used called term pre-manifest that has been used to describe the group of patients with prodromal HD who are felt by their clinician to be developing the extrapyramidal motor signs. The transition from pre-manifest status to a diagnosis of manifest HD is considered the starting point of the disease, and after this stage, irreversible destruction occurs in progressive multiple domains. The Unified Huntington's Disease Rating Scale (UHDRS) is the most commonly used large-scale tool and is used to evaluate the motor, cognitive, behavioral, emotional, and functional components of HD (Figure) (Huntington, 2003). The total motor score (TMS) is a scale within the subscale UHDRS and is used in diagnosis and progression from the onset of the disease (Shoulson & Fahn, 1979). Based on the TMS, the clinical assigns a diagnostic confidence score ranging from 0 to 4. A score of 4 represents the onset of manifest disease. Once a diagnosis is made, the disease is said to progress through five stages that are based on the total functional capacity (TFC) subscale of the UHDRS. This assesses a patient's ability to work, and manage household finances, chores, and activities of daily living, and the level of care required, giving an overall score of 13 (fully independent) to 0 (fully dependent). The score relates to disease stages I–V (originally the Shoulson–Fahn staging system) (Shoulson & Fahn, 1979). More broadly, the terms early, moderate, and advanced disease are helpful in clinical practice.

Chorea

Chorea in HD is the core-stone finding in adult that defined as arrhythmic, rapid, jumping, or fluent, simple or complex involuntary movements of small amplitude, usually involving the distal extremities and generally seen more clearly in the early stages, but in later stages, facial grimacing, eyelid elevation, neck , shoulder, trunk, and leg movements may accompany it. Chorea typically increases in frequency and amplitude over time and may peak about 10 years after disease onset and then plateaus and lessens. Chorea is rated in one of seven body regions (i.e. face, mouth, trunk, and extremities). The total chorea score is the sum of the scores for each body region and can range from 0 to 28. The rating calculation is as follows: 0 = absent, 1 = slight intermittent, 2 = mild/common or moderate intermittent, 3 = moderate /common, and 4 = marked/prolonged.

Dystonia

Dystonia causes temporary or permanent abnormal postures and movements due to involuntary, persistent, or repetitive, twisting, and rotating muscle contractions and develops as a result of simultaneous contractions of muscles (agonist and antagonist muscles) working opposite each other to perform purposeful motor behaviors or to maintain a certain posture. Contraction is usually slow, and staggering. But sudden and rapid contractions called choreic or myoclonic dystonia can also be seen. Dystonia occurs or increases when the affected body area is used voluntarily, especially at the beginning of the disease. During voluntary movements of another body region, the dystonic region contracts more (the "overflow" or "overflow" phenomenon) and may disappear completely during sleep. Dystonia is especially quite common in the juvenile and adult-onset rigid-dystonic variant of HD. Trunk dystonia can occur as an early symptom and cause severe back pain (Schiefer & et al., 2015). Dystonia is rated in one of five body regions (i.e. trunk and extremities). The total dystonia score is the sum of the scores for each body region and can range from 0 to 20. The rating calculation is as follows: 0 = absent, 1 = slight intermittent, 2 = mild/common or moderate intermittent, 3 = moderate /common, and 4 = marked/prolonged.

Bradykinesia

Bradykinesia is defined as difficulty in initiating movements, slowness and difficulty in execution, and impoverishment of movements. Loss of facial expressivity, absence of arm swing, difficulty with finger tapping and rapid alternating movements, and gait slowness are quite common and worsen with disease progression. These features, especially when combined with the impaired postural reflexes that occur in HD, can lead to greater problems than the more dramatic chorea seen earlier on (Rosenblatt & et al., 2012) Clinically, bradykinesia may be associated with chorea and dystonia, in which case it may be difficult to recognize. In addition, treatments to treat chorea can hide bradykinesia. Bradykinesia is calculated as the total chorea score and can range from 0 to 4. The rating calculation is as follows: 0 = normal, 1 = minimally slow(normal), 2 = mild but slow, 3 = moderately slow, some hesitation, 4 = markedly slow, long delays initiation.

Other Motor Disorders

Tics are generally defined as sudden, involuntary movements (motor tic) or sounds (vocal tic) that appear short, non-rhythmic, stereotypical, and aimless, involving one or more muscle groups based on normal movement. On clinical examination, tics may mimic choreic and dystonic movements. Respiratory and vocal tics can produce sniffs, grunts, moans, or coughs.

Myoclonus is a sudden, short-lived (<100ms), lightning-fast involuntary movement in the form of throwing, or jumping. Myoclonus may involve the extremities, face, and trunk, and cannot be voluntarily prevented. Myoclonic contractions may occur spontaneously at rest, or only with a specific sensory stimulus (reflex myoclonus), or during voluntary movements (action myoclonus). Myoclonic movements are classified according to the anatomical formations they originate from, the body regions they affect, and their etiology.

Tremors are involuntary, rhythmic oscillations resulting from alternating or synchronous contraction of the reciprocal muscles that move a body part. Tremor depends on the affected area (head, jaw, elbow, vocal cords, lower or upper extremities, body), relation to the movement (resting, postural, actional, intentional), frequency (low: less than 4 Hz; medium: 4-7 Hz); high is defined by more than 7 Hz) and amplitude (fine, coarse). Clinically, rest tremors, postural

tremors, or intentional tremors with voluntary movement are frequently observed in HD. Myoclonus and tremor are much more commonly seen in Juvenile onset HD or young adults.

Rigidity is characterized by an increase in muscle tone and a decrease in passive mobility, and may occur early in juvenile or adult akinetic/rigid HD, but is also common in advanced HD. Rigidity is rated in the upper extremities (i.e. right and left arms). The total rigidity score is the sum of the scores for each arm and can range from 0 to 8. The rating calculation is as follows: 0 = normal, 1 = slight or present only with activation, 2 = mild-r moderate, 3 = severe, full range of motion, and 4 = severe with limited range.

Progressive voluntary loss of motor control begins in the early stages of the disease and progresses in correlation with disability. Slow initiation and velocity of saccadic eye movements are the early signs of voluntary movement impairment, and difficulty with finger and manual dexterity may appear in the early stage. On physical examination, the first finding is the slowing of finger tapping and confusion and the slowing of fast alternating movements of the hands. In the advanced stages, there is a total loss of skill in voluntary movements. In addition to hyperreflexia and extensor plantar reflexes, patients are akinetic, rigid, and dystonic. Symptoms may include the “milkmaid's grip” or insufficient pressure on the accelerator pedal while driving which manifests itself as a difficulty in writing, dropping items, and insufficient/not being able to perform fine motor movements. In UHDRS, ocular pursuit, saccade initiation, saccade velocity, dysarthria, tongue protrusion, finger taps, pronation/supination, Luria, gait, tandem, and retropulsion/pull are rated in one of the related movement body regions in the aspect of voluntary muscle control capability and balance/gait evaluation. For ocular movement; horizontal and vertical direction and for pronation/supination: right and left arms are evaluated. The total scores are the sum of the score for each body region and can range from normal (0) to 4 (total dysfunctionality).

Behavioral Assessment

The behavioral assessment measures overall thought content/orientation and the frequency and severity of symptoms associated with coping with daily problems. The total behavior score is a domain of UHDRS and represents the frequency and severity of 11 items, which are rated from zero (rarely/absent) to four (almost always/severe). The items assess depression, anxiety, aggression, psychosis, and other behavioral abnormalities. The behavioral score ranges from 0 to 88, with higher scores indicating more severe psychiatric abnormalities.

Cognitive Assessment

Cognitive impairment occurs as a result of dysfunction of the extensive neural network specialized for a certain cognitive function. Dysfunction of the episodic memory neural network located in the limbic and para-limbic areas and their subcortical components leads to amnesia, dysfunction of the language network located in the front-parietal-temporal neocortical areas of the left hemisphere and their subcortical components leads to cognitive impairment in the form of aphasia. Cognitive impairments in HD encompass a broad variety of cognitive skills, including learning and memory, perceptual skills, executive efficiency, and language. Cognitive impairments may emerge years before disease onset (Paulsen & et al., 2008, Stout & et al., 2011) that range from subtle cognitive deficits to obvious complete disability. Learning and memory problems are among the early cognitive impairments of HD. There was no evidence of congenital cognitive dysfunction in HD, but studies suggest that subclinical cognitive changes may precede motor signs in patients approximately 15 years. Memory problems are one of the frequently reported symptoms in HD, and people mainly have difficulty learning new things and remembering previously learned information (Paulsen & et al., 2008,

Peavy, Jacobson & Goldstein, 2010). The underlying pathology is thought to be the slowing of the processing speed in the recording memory and the inability to organize the information (Rosenblatt & et al., 2012). In recent studies, it is found that the main problem in HD is the slowdown in processing speed in accessing and remembering information, rather than the disorder in the information recording process (Rothlind & et al., 1993). The longitudinal study PREDICT-HD followed a cohort of over 800 patients and found certain cognitive domains were affected even in pre-manifest disease, including verbal learning/memory, attention–information integration, sensory-perceptual processing, and motor planning/speed (Harrington & et al., 2012). The TRACKHD study found evidence of deterioration in early-stage HD (Tabrizi & et al., 2011, Tabrizi & et al., 2013). concerning tests of visual attention, psychomotor speed, and visuomotor and spatial integration. Essentially, implicit memories are affected, which domain is responsible for managing skills and coordinated movements such as riding a bike or playing musical instruments (Novak & Tabrizi, 2011). There may be some overlap with psychiatric symptoms in terms of disinhibition and impulsive behaviors, with an accompanying lack of insight (Duff K & et al., 2010). Semantic memory remains relatively preserved (Paulsen & et al., 2001).

Neuropsychiatric Assessment

The diagnosis of HD Is mainly based on the presence of motor symptoms, cognitive dysfunctions, neuropsychic symptoms, and a decrease in daily functioning are seen as the most important predictors of comorbidity (Sinanović, 2020, Ross, Aylward & Wild, 2014, Ishihara, Oliveri & Wild, 2021) and may occur years before the onset of motor symptoms (van Duijn, Kingma & van der Mast, 2007). The structures held responsible for neuropsychiatric pathologies are estimated to be in the basal ganglia-thalamocortical circuits, especially in the pre-manifest stage of cranial involvement (van Duijn, Kingma & van der Mast, 2007, Martinez-Horta & et al., 2016). Personality and behavioral changes, which can also be described as hypo frontal or executive dysfunction syndrome, can be observed in almost every patient in the premotor stage. These signs and symptoms, which can be roughly defined as apathy, irritability, impulsivity, and obsessiveness, can cause great disability in the family and social life of the person (Ishihara, Oliveri & Wild, 2021, Martinez-Horta & et al., 2016, Nance & et al., 2011).

Mood Disorders

Depressive symptoms are among the most common psychiatric disorders in HD (Morris, 1991), its prevalence has been reported in a wide range of 9-63%, and it has been reported that approximately 50% of patients will experience depression at any stage of the disease (Paoli & et al., 2017). Martinez-Horta et al. tried to determine the estimated relative risks (odds ratio) of neuropsychiatric symptoms in HD cases in the presymptomatic, just before the symptomatic period, and it was reported that depression was found in 65% of the cases (Martinez-Horta & et al., 2016). This result has been reported that depression in HD may be associated with neurodegeneration (Slaughter, Martens & Slaughter, 2001) and early cell loss in the medial caudate, which has connections with limbic structures (Gubert, Renoir & Hannan, 2020).

The high prevalence of depression in HD is because of a biological predisposition associated with psychological and psychosocial factors (Goh & et al., 2018). It is known that depression is one of the earliest onset symptoms of the disease and is considered among the core symptoms of the disease (van Duijn, Kingma & van der Mast 2007, Paoli & et al., 2017). It has been reported that, unlike depression in the general population, there is no significant difference in the prevalence of depression between the genders (Eddy, Parkinson & Rickards,

2016), and the age of onset for depression in HD is approximately 14 years earlier than that in the general population (Paoli & et al., 2017).

Apathy

Apathy can be defined as a decrease in the level of consciousness, cognitive impairment, or decrease in motivation that is not related to emotional stress (Levy & et al., 1998). Lack of interest, psychomotor retardation, lack of energy and motivation, and lack of motivation, which is not accompanied by sadness, dysphoria, and vegetative symptoms (i.e. insomnia, fatigue, lack of attention), is observed (Goh & et al., 2018). Apathy is one of the most common neuropsychiatric manifestations in HD (Camacho, Barker & Mason, 2018). Studies report its prevalence in the presymptomatic period to be 11-64%, and in the symptomatic period between 47-76% (Paulsen, & et al., 2008, Martinez-Horta & et al., 2016) and thought to be mainly related to global and executive cognitive performance (Goh & et al., 2018). In the study of Martinez Horta et al. (Martinez-Horta & et al., 2016), apathy was found with a frequency of 32% in mutant gene carriers long before the symptomatic stage and 62% in early-stage HD.

Anxiety

Anxiety can be defined as a causeless state of uneasiness, and fear accompanied by somatic symptoms. The prevalence of anxiety in symptomatic HD cases is reported as 34-61% (van Duijn, Kingma & van der Mast, 2007). The prevalence is reported to be 0-17% in mutant gene carriers before the presymptomatic period (Dale & van Duijn, 2015, van Duijn, Kingma & van der Mast, 2007) with mutant gene carriers in the presymptomatic stage. In studies comparing non-carriers (Duff & et al., 2010, Marshall & et al., 2007), more anxiety symptoms were found in gene carriers. It has been reported that anxiety symptoms in HD are not associated with age, gender, number of CAG repetitions, motor functionality, cognitive skills, apathy, and disease duration/progression (Dale & van Duijn, 2015). However, studies are reporting that anxiety is associated with depression, agitation, and irritability (Paulsen & et al., 2008, Nimmagadda & et al., 2011). In a study with 2106 HD mutant gene carriers, anxiety was reduced. It has been reported that it is an independent predictor of suicidal ideation, but this predictor disappeared after a 4-year follow-up (Hubers & et al., 2013).

Suicide

In a study, suicidal ideation, suicide attempt, and suicide rates were included in HD cases (Kachian & et al., 2019), the rate of suicidal ideation in HD was 20-30%, the rate of suicide attempts was 7-10%, and the suicide rate was 4.8%-6%. In the world population, these rates have been reported as 8-24.9%; 1.3-3.5%; 1.5-3 %, respectively (Kachian & et al., 2019). In a recent study examining suicide in frontotemporal dementia (FTD) and HD, 267 individuals with HH or FTD from 106 families were included, and completed suicide was found in 7 out of 160 individuals with HD (6 out of 59 families) (Nock & et al., 2008). Compared to the general population, the risk of death by suicide was calculated to be 400 times higher in the HD group, and the mean age at suicide was reported as 52.5 (35-73 years). In the same study, suicide was observed in 1 of 15 families (in FTD and HH families). This rate is more common in families with HD and is seen in up to 30% (Nock & et al., 2008). In the large sample study of Rodrigues et al. (Rodrigues & et al., 2017) (n: 5164), the completed suicide rate was found to be 6.6%. Although studies indicate different rates, it is clear that suicide, suicidal ideation, and attempt are more common in HD than in the general population and even other chronic neurodegenerative diseases (Ishihara, Oliveri & Wild, 2021), which should be kept in mind and questioned in the follow-up of these patients. Studies are reporting that the male gender is a risk

factor for suicide and the female gender is a risk factor for suicidal ideation and behavior (Solberg & et al., 2008). While there is no relationship between the number of CAG repeats in the mutant gene and suicidal behavior (Hubers & et al., 2013), data are showing that the stage of the disease and different aspects of suicidal behavior may be related.

Irritability, Aggression, Impulsivity

There are neurobiological mechanisms (degeneration in the striatum and orbitofrontal-subcortical circuits) related to HD in its etiology, as well as psychological causes such as cognitive overload caused by progressive cognitive losses (Chu & et al., 2019). Irritability, which is often described as the first sign of the disease in patients before the motor symptomatic period (van Duijn & et al., 2008), is seen in the range of 35-73% in HD (Paoli & et al., 2017). Irritability, impulsivity, and aggression are considered interrelated clinical manifestations, and the prevalence of aggression in HD is reported to be between 22-66% (Goh & et al., 2018). In a follow-up study conducted with individuals at genetic risk and lasting approximately 4 years, irritability, and hostility were found to be significantly worsened in those with mutant gene carriers, and was found that this increase was not associated with the number of CAG repeats (Kirkwood & et al., 2002). In the study of Reedeker et al. (Reedeker & et al., 2012b), the number of CAG repeats was found to be associated with irritability. Van Duijn et al. (van Duijn & et al., 2014) reported that irritability/aggression is associated with male gender, young age, depression, psychosis, and suicide attempt history.

Obsessiveness/Perseveration

The prevalence of obsessive and compulsive symptoms in HD is reported to be between 20-50% (Goh & et al., 2018). Perseveration is defined as the uncontrolled repetition or persistence of a response regardless of the cause or context from which it originated (Serpell, Waller & Fearon, 2009). It has been reported that corticostriatal circuits are affected by perseveration and obsessive-compulsive symptoms (Paoli & et al., 2017). Perseverative behaviors are more common in HD, with rates up to 75% reported (Oosterloo & et al., 2019). Obsessive and compulsive symptoms are also more common in mutant gene carriers in the premotor stage compared with the general population (van Duijn & et al., 2008). It was determined that aggressive and contagious obsessions and control rituals were observed most frequently (Goh & et al., 2018). van Duijn et al. (van Duijn & et al., 2014) found that the prevalence of perseverative/obsessional thinking and compulsive behavior increased with the progression of the disease, while the prevalence was 4.5% in the first stage of the disease, it increased to 25% in the third stage.

Psychosis

Psychotic symptoms in HD compared to other neuropsychiatric conditions are seen more rarely and the prevalence is reported to be 3-11% (46%). The prevalence of delusions and hallucinations in patients with HD was reported as 10-11.5% and 1.9-3%, respectively (Paulsen & et al., 2011). In the study of Jaini et al. (Jaini, Yomtoob & Yeh, 2020), in which they evaluated 7966 patients diagnosed with HD in the motor symptomatic period, it was found that 12.95% of the patients had a history of psychotic symptoms, the mean age of onset of psychosis was 48, and the motor symptoms of HD coincided with the age of onset. It has also been reported that psychotic symptoms may begin in the premotor stage (Kar & et al., 2016). Psychosis that begins before motor symptoms is often interpreted as a precursor to the onset of motor symptoms (Ross, Aylward & Wild, 2014).

Another psychiatric disorder that we can see in HD is sexual dysfunction. Although sexual dysfunctions are often in the form of decreased sexual desire and inhibition of orgasm, it has been reported that paraphilic behaviors may develop in some patients (Paoli & et al., 2017). In the systematic review of Szymus et al. (Szymuś & et al., 2020), the most common sexual disorders are; hypoactive sexual disorder (53-83%), hyperactive sexual disorder (6-30%), erectile (48-74%) and ejaculation (30-60%) dysfunction, lubrication problems (53-83%) and orgasm disorders (35-78%) were found.

Neuroradiological approach to Huntington's disease

The most prominent pathology in HD is progressive atrophy mainly in the caudate nucleus and putamen, and to a lesser extent, in the globus pallidus, cortex, thalamus, and subthalamus. Neuropsychological findings have been traditionally attributed to pathology in cortical structures, while motor deficits have been associated with striatal pathology. Although the basal ganglia are considered to be the area responsible for basic motor symptoms, recent studies have demonstrated important anatomical and functional sub-systems in basal ganglia structures(Alexander, DeLong MR & Strick, 1986). DeLong and coworkers (Brandt & Butters, 1986) described five segregated "loops" that connect fronto-cortical areas with different basal ganglia structures. The putamen has functional and anatomical connections to motor-related cortical structures, particularly the supplementary motor cortex. The caudate nucleus, on the other hand, has no fiber connections with the motor cortex, except for the frontal eye fields. Its major cortical connections are with frontal areas with established cognitive functions, especially the dorsolateral and orbital frontal cortices, and with limbic cortical areas related to emotional function. (Alexander, DeLong MR & Strick, 1986). In another study, measurements of cortical and subcortical atrophy were made in 34 patients, and significant correlations were found between the bicaudate ratio (BCR) and an eye movement scale ($r = 0\ 44$, $p < 001$), and activities of daily living scale ($r = 0\text{-}57$, $p < 0\text{-}001$) and the Mini-Mental State Exam besides, detailed neuropsychological evaluation in 18 patients were made and significant correlations between the BCR and Symbol Digit Modalities test, and parts A and B ($p < 0\ 0001$) of the Trail Making Test were found. While this result supports the importance of the caudate nucleus in cognitive and oculomotor functions, it has been determined that it is unrelated to motor controls (Sergıo & et al., 1988). It is known that difficulty in initiating saccades, slowing of saccades, and fixation instability are observed in HD (David & et al., 1987), which was shown in a study to be closely related to caudate atrophy (Sergıo & et al., 1988). In another study conducted during a similar period, Young et al. found a significant correlation between basal ganglia (caudate and putamen) metabolism and abnormal eye movements (Young & et al., 1986). The presence of strong connections between the caudate nucleus and other regions involved in oculomotor movement may explain the influence of caudate atrophy upon eye movement functions, such as the frontal eye fields and the substantia nigra pars reticulata. Sax et al. (Sax & et al., 1983) also found significant correlations between BCR and several neuropsychological tests, with the highest being between the BCR and the Symbol Digit Modalities Test. Fisher et al. (Fisher & et al., 1983) demonstrated that Huntington's disease patients are substantially impaired in procedures such as Porteus Mazes, Wisconsin Card Sorting Test, and Stroop Test, which, like Trails B, involve visuospatial planning and rapid mental processing. Also, they reported that the ability of cognitive organizations to initiate and develop a cognitive strategy is impaired in the early period in HD, and they suggested that this regression may be related to progressive caudate atrophy.

In extensive studies, neuronal loss in neostriatum proceeds from medial to lateral and from dorsal to ventral, a pattern confirmed by others has been reported (Brandt & Butters, 1986). In a case report, neostriatal atrophy was found primarily in the putamen in a postmortem

study in a patient who was in the pre-manifest stage of HD (Wijeyekoon & Barker, 2011). In more advanced cases, abnormalities are usually detectable on clinical readings of MRIs or CTs, which often reveal widespread cortical and subcortical atrophy, such as described in one MRI study that reported qualitative subcortical atrophy in 4 patients with HD (Simmons & et al., 1986). Studies are showing that volumetric measurement in Mild HD is more sensitive than qualitative or linear measurements. Volumes of caudate and putamen are difficult to quantify using CT, however, due to its relatively poor resolution of gray and white matter. MRI is superior for quantifying gray matter (Jernigan & et al., 1991). There has been one previous study using quantitative MRI in HD (Jernigan & et al., 1991). Another study (Montoya & et al., 2006) reported that cortical and subcortical atrophy was observed in morphometric evaluations in CT or MRI scans in patients with severe dementia diagnosed with advanced-stage HD. In this study, volumes of the caudate and lenticular nucleus (putamen and globus pallidus) were measured and it was found that caudate volume reduction was greater than that of the lenticular nucleus. In one study, volumes of caudate nucleus and putamen and bicaudate ratios (BCR) from magnetic resonance images were measured in 15 patients, and the region showing the greatest atrophy was the putamen, which was reduced 50.1% in mean volume in HD patients compared with control subjects ($p < 0.000001$) was detected. In the same study, caudate volume was reduced by 27.7% ($p = 0.004$) and BCR was increased by 28.5% in HD patients ($p = 0.0002$) (Harris & et al., 1992).

Neuropathological Evaluation of Huntington's Disease

The progressive degenerative neuropathological process is topographically variable and related to the deleterious action of the unstable CAG repeat expansion (Andrew & et al., 1993, Duyao & et al., 1993, Meyer A, Beck F & McLardy, 1947). The expression of the degenerative process differs not only among distinct anatomical compartments but also within specific brain compartments (e.g., cerebral cortex, white matter, striatum, pallidum, thalamus, brainstem, cerebellum), or systems (e.g., basal ganglia, limbic) system) (Selemon, Rajkowska & Goldman-Rakic, 2004, Shoulson & Young, 2011). The involvement and the evolution of the neurodegenerative changes in the striatum (caudate nucleus, putamen), and pallidum (paleostriatum) strikingly underscore the differential vulnerability regional occurring in HD within this discrete, relatively small subregions of the brain (Estrada-Sanchez & Rebec, 2013, Rüb & et al., 2004a). The vulnerability of the striatum was thought to be proportional to the IT15 CAG size in HD (Penney, Vonsattel & MacDonald, 1997, Furtado, Suchowersky & Rewcastle, 1996). Vonsattel grading system can be used to classify degeneration into five levels and grades in ascending order of striatal degeneration severity (Vonsattel), the affection of the cerebral cortex during the course of HD.

In HD, cortical neuronal loss is most evident in isocortical neuronal layers III, V, and VI (Rüb & et al., 2004a, Fennema-Notestine, Archibald & Jacobson, 2004, Sheperd, 2003). According to current pathophysiological ideas, the affection of the cerebral cortex not only represents the morphological correlate of these psychiatric, neuropsychological, and neurophysiological manifestations in HD but may at least be jointly responsible for the occurrence of involuntary choreatic movements (Walker, 2007).

The occurrence of chorea has been seen as a result of striatal degeneration (Rüb & et al, 2004a, Walker, 2007b, Voogd, 2003), but studies have reported that cortical pathology has a pathophysiological role in the formation of chorea (Scherzed & et al., 2012). Since comprehensive analysis revealed that lesions of the caudate nucleus, putamen, or pallidum result in choreatic movements only in the minority of affected individuals, the manifestation of chorea is currently supposed to result from dysfunctional corticostriatal projection neurons

and/or their impaired intra-telencephalic input in HD (Rüb & et al, 2004a, Brodmann & et al, 2010). The first volumetric studies of serial tissue sections in brain tissue in postmortem studies with HD yielded atrophy and volume loss of distinct cortical areas and regions (Wiegand & et al., 1991, Rüb, Hoche & Brunt, 2013a).

The typical distribution pattern of brain neurodegeneration is thought to be the result of an anterograde, retrograde, or transneuronal and topographically highly ordered spread of the underlying pathological process throughout the brain via interconnecting brain fiber tracts (Rüb, Brunt & Deller, 2008a, Rüb, Jen & Braak, 2008b). A systematic investigation of the cerebellum displayed consistent atrophic changes (i.e., reduction of its entire volume and the surface area of its arbor vitae; atrophy of the lobules of the anterior and posterior lobes; widened primary fissure) (Rüb, Hoche & Brunt, 2013a). In the microscopic examination, diffuse neuronal loss was observed in the cerebellar cortex and deep cerebellar nuclei, and especially consistent and selective loss of Purkinje cells was detected while the molecular and granular cell layers were typically spared (Rüb, Hoche & Brunt, 2013a).

The close parallels between the pathological features of oculomotor dysfunction and damage of the nuclei of the premotor oculomotor brainstem network in humans and nonhuman primates showed that the neurodegenerative process in HD also affects these targets (Rüb, Brunt & Deller, 2008a, Rüb, Jen & Braak, 2008b). As a result, these new findings in premotor oculomotor nuclei of the pons, pontomedullary junction, and medulla oblongata for the first time offered adequate explanations for a variety of oculomotor dysfunctions that may occur in HD patients (Rüb & et al., 2014a).

During the neuropathological progression of HD, the processes also begin in the select nuclei of the brain stem (i.e., dopaminergic and GABAergic substantia nigra, auditory superior olive, lateral vestibular nucleus, cerebellar inferior olive) (Rüb & et al., 2014a, van Wamelen & et al., 2014). This presumptive diagnosis has been evaluated in genetically and clinically proven HDs by systematic pathoanatomical studies and showed disease signs possibly related to brainstem damage (i.e., broad-based gait, gait imbalance, dysphagia, slowed horizontal saccades, etc,) (van Wamelen & et al., 2014). Further results of postmortem studies suggested that several additional subcortical regions (e.g., amygdala, hypothalamus, subthalamic nucleus, claustrum), which are intimately linked with the well-known targets of the disease process of HD via fiber tracts (e.g., prefrontal cortex, entorhinal and transentorhinal regions, thalamic mediodorsal nucleus and centromedianparafascicular complex, striatum), may also undergo neurodegeneration during HD (van Wamelen & et al., 2014).

Current Treatment Approaches in Huntington's Disease

Treatment Strategies Targeting Motor Findings

Chorea

Motor manifestations such as hyperkinesia or chorea are treated with dopamine receptor-blocking or depleting agents. The most commonly used drugs for chorea are typical or atypical neuroleptics (dopamine receptor blocking) and tetrabenazine (dopamine depleting). An extensive review of the medications used has been studied by Bonelli (Bonelli & Wenning , 2006, Bonelli & Hofmann, 2007).

In 2008 the Food and Drug Administration approved tetrabenazine (Xenazine®) for the relief of chorea. The mechanism of tetrabenazine is the depletion of dopamine release by presynaptic striatal neurons, which can cause sedation, depression, akathisia, and the worsening

of voluntary motor control. About 20% of individuals in the placebo-controlled trial experienced a new onset or worsening of depression, and there was one completed suicide (Yero & Rey, 2008). Besides, tetrabenazine may prolong the corrected QT interval (QTc), and caution is advised when used in combination with other drugs or medical conditions that potentially prolong the QTc. Physicians are also cautioned about the potential risk of tardive dyskinesia or neuroleptic malignant syndrome. The dose of tetrabenazine should be halved for people with HD who are also taking strong CYP2D6 inhibitors, such as fluoxetine, paroxetine, and quinidine (Yero & Rey, 2008). Also, neuroleptics block dopamine at the striatal post-synaptic receptor (Lyon & et al., 2011). Typical neuroleptics such as haloperidol or fluphenazine are quite effective. Some atypical neuroleptics, such as olanzapine and risperidone may also be effective. The atypical neuroleptics, quetiapine, and clozapine do not block dopamine D2 receptors and are generally ineffective for chorea. Side effects of neuroleptics include apathy, sedation, akathisia, worsening of voluntary motor control, tardive dyskinesia, and neuroleptic malignant syndrome.

Dystonia

Pharmacologic treatment of dystonia in HD may include benzodiazepines, baclofen, and sometimes dopaminergic agents developed for Parkinson's disease. Botulinum toxin injections can be quite effective for focal dystonias. Careful monitoring for hallucinations and psychosis is necessary when using dopaminergic agents. Some people with HD, with severe dystonia, benefit from braces, pads, or splints for affected joints; a physical or occupational therapist can assist in the evaluation and dispensing of appropriate equipment.

Bradykinesia

Bradykinesia in people with Juvenile onset HD, and adults with the rigid/dystonic form of HD, may improve with treatment with amantadine or carbidopa/levodopa.

Other Movement Disorders in HD

Tics can be reduced by benzodiazepines, SSRIs, neuroleptics, and possibly by off-label use of tetrabenazine. In myoclonus and tremor, clonazepam is quite effective. A resting parkinsonian tremor may appear as a side effect of neuroleptic therapy for psychosis or chorea in persons with HD. Neuroleptic drug dose reduction or change to an atypical agent should be considered. Rigidity may be improved by the reduction or cessation of tetrabenazine or neuroleptic drugs, or by benzodiazepines, baclofen, and possibly by dopaminergic drugs. Loss of voluntary motor movement and stool disturbances are difficult to treat and should be evaluated with personalized physical therapy. For this purpose, dopaminergic stabilizing treatment strategies have been developed, but it is still in the testing phase. As gait difficulties increase, the use of proper footwear and adaptive equipment should be encouraged. Some individuals may be able to self-propel in a standard wheelchair using their arms and legs. Those with difficult chorea or trunk dystonia may benefit from a custom wheelchair with a reclining back, elevating leg rests, removable armrests, and a pommel (“saddle”) seat to prevent sliding out. Also, simple “word boards” placed on the lap can help some people with HD to communicate simple ideas and questions. A speech-language pathologist should assess the individual with dysphagia periodically and suggest adaptations that will improve swallowing and minimize choking. Eating slowly, avoiding distractions during mealtime, adjusting food textures, and using adaptive equipment are all helpful in reducing choking. Family members should be taught the Heimlich maneuver.

Treatment Strategies Targeting Neuropsychiatric Findings

Mood Disorders

Depression is the most common neuropsychiatric symptom and since it negatively affects the quality of life and functionality in HH mutant gene carriers (Ready & et al., 2008, Gibson Ready & et al., 2022) and increases the risk of suicide (Kachian & et al., 2019), it must be treated. In the presence of mild depression without cognitive impairment, psychotherapy may be an appropriate option (Stahl & Feigin, 2020). It has been found that psychoeducation, including cognitive-behavioral therapy (CBT) techniques, has a positive effect on depression, anxiety, and coping skills in symptomatic and presymptomatic cases (n:41) (A'Campo, Spliethoff-Kamminga & Roos, 2012, Silver, 2003). As drug therapy, selective serotonin reuptake inhibitors (SSRI), serotonin noradrenaline reuptake inhibitors (SNRI), mianserin, or mirtazapine are recommended in cases where sleep disturbance is accompanied. In the presence of recurrent depression, mood-stabilizing agents can be used in addition to antidepressants (Adrissi & et al., 2019, Bachoud-Lévi & et al., 2019). Electroconvulsive therapy should be considered as an option in the presence of severe depression that is resistant to drug therapy, has a high risk of suicide, or is accompanied by psychotic symptoms (Adrissi & et al., 2019, Bachoud-Lévi & et al., 2019). In the mania treatment strategy, mood stabilizers such as valproate and carbamazepine can be used (Paoli & et al., 2017).

Apathy

Apathy is one of the most common neuropsychiatric manifestations in HD. In the case series of A'Campo et al. (A'Campo, Spliethoff-Kamminga & Roos, 2012) with HH in six symptomatic stages, Remotivation Therapy was applied for apathy and it has been reported that improvements in interest, awareness, attention, frustration tolerance, reading skills, and verbal communication are achieved. Although studies on methylphenidate, atomoxetine, modafinil, amantadine, and bromocriptine do not contain satisfactory results (Scheuing & et al., 2014).

Anxiety

Cognitive-behavioral therapy and psychoeducation using these therapy components can be effective in reducing the level of anxiety in cases where cognitive dysfunction is not evident in the early period (A'Campo, Spliethoff-Kamminga & Roos, 2012). In the coexistence of depression and anxiety, drugs from the SSRI and SNRI groups can be used, but in severe cases, benzodiazepines can be added to the treatment for a short time, warning about the risks of falling or worsening of symptoms (Bachoud-Lévi & et al., 2019). If there is no response to an SSRI agent, another SSRI can be tried, or if an SNRI agent or obsessive symptoms are accompanied, clomipramine can be used. Mirtazapine is among the options in cases where insomnia is accompanied, and olanzapine (Leroi & et al., 2002) in patients with unsuccessful other treatment options and chorea symptoms.

Suicide

When depression or suicidal ideation is detected in a patient using tetrabenazine, deutetrabenazine, amantadine, or riluzole, which are safer areas for the treatment of chorea, may be preferred, or in appropriate cases, clinical symptoms may be improved by adding

antidepressants to tetrabenazine (Squitieri & et al., 2001, Bayram, Mercan & Akbostancı, 2015).

Irritability, Aggression, Impulsivity

There is no specifically approved treatment option for the treatment of irritability in HH yet, but there are some treatment algorithms (Groves, 2017). To reduce irritability, it is recommended to resort to behavioral methods first. In the treatment of irritability, it is seen that drugs from the SSRI group are frequently recommended (Bachoud-Lévi & et al., Harris & et al., 2020). It is reported that the dose should be increased up to the highest recommended dose of the relevant drug. Mirtazapine or mianserin can be added to the treatment, especially in patients with accompanying insomnia, when there is no adequate response from the SSRI (Bachoud-Lévi & et al., 2019). Second-generation antipsychotics are often second-line agents, and in cases unresponsive to SSRIs, accompanied by psychosis, marked aggression, impulsivity, and accompanied by hypersexuality, second-generation antipsychotics are the first choice (Groves, 2017). Besides being effective in the treatment of chorea and irritability, antidopaminergic agents can increase the decrease in cognitive performance (Harris & et al., 2020). Antiepileptic agents, which are used as mood stabilizers, are often preferred in the third row, and it is recommended to be used alone or as a combined treatment when there is no adequate response to antidepressants or antipsychotics (Scheuing & et al., 2014).

Obsessiveness/Perseveration

In the treatment of both obsessive and compulsive symptoms and perseverative behaviors, especially in patients with anxiety, SSRIs are recommended in the first place (clomipramine, a tricyclic antidepressant, is often included in this group), and olanzapine and antidepressants based on perseveration accompanied by irritability. risperidone seems to be recommended (Scheuing & et al., 2014).

Psychosis

It has been reported that psychosis in HH clusters in families, and as the number of CAG repeats increases, both motor symptoms and psychosis tend to start at an earlier age (Tsuang & et al., 2000). In the presence of psychotic symptoms such as hallucinations and delusions, second-generation antipsychotics are the first-line recommended agents and the power of evidence is at the level of expert opinion (Scheuing & et al., 2014). Although clozapine is often recommended in patients who do not respond to other antipsychotic agents (van Duijn, Craufurd & Hubers AA, et al., 2014), it may be preferred first in patients with akinetic HD who have severe Parkinsonian symptoms (Scheuing & et al., 2014).

Other Psychiatric Disorders

Behavioral recommendations regarding sleep hygiene should be implemented for all types of sleep problems. Modafinil can be tried in case of excessive daytime sleepiness (Blackwell & et al., 2008). Melatonin receptor agonists (such as ramelteon and agomelatine) may be beneficial in the case of insomnia (Herzog-Krzywoszanska & Krzywoszanski, 2019). Sedating antidepressants such as mirtazapine and trazodone are also agents that can be used. Olanzapine or quetiapine can be preferred as antipsychotics. Clomipramine may be a choice for patients with concomitant obsessive-compulsive symptoms.

Hypersexual sexual disorders can be considered behavioral problems that develop based on disinhibition and impulsivity (Morris, 1991, Craufurd & Snowden, 2002) in the treatment of antipsychotic agents may be considered in the foreground.

Therapeutic Strategies Targeting Genetic Mutations

HD is mainly caused by a mutation in the HTT gene encoding the Htt protein, and the treatment strategies developed mainly target HTT transcription and its mRNA translocation. For this purpose, among the treatment options, FDA-approved antisense oligonucleotide nusinersen that modulate gene expression and increase the production of survival motor neuron (SMN) protein used intrathecally in patients with spinal Muscular Atrophy (SMA) has been considered (Hoy, 2017).

The therapeutic strategies which target mHtt production can be divided into two major classes: drugs that interact with the HTT gene, such as antisense oligonucleotides (ASOs) or RNA interference (RNAi) compounds, which accelerate the degradation of the transcript, and small molecules which alter mRNA splicing; and agents that directly interact with the DNA, such as zinc finger transcriptional repressors (ZFTRs) and CRISPR/Cas9 (clustered regularly inter-spaced short palindromic repeats/CRISPR-associated protein9)-based tools for genetic editing (Pulecio & et al).

Therapeutic Strategies Targeting Cell Loss

Neuronal loss due to HD pathology could be replaced by using stem cell therapies, which could also provide pro-survival factors and improve regeneration. The most adv, 2017anced stage among stem cell-based therapeutic approaches is an allogenic mesenchymal therapy using human immature dental pulp stem cells developed by the Brazilian company Cellavita (Gonzaga & et al., 2022). In phase 1 clinical trial (NCT02728115/SAVEDH, preliminary results (Macedo & et al., 2021) justified the application for a phase 2 clinical trial (NCT0325253). Dose-response Evaluation of the Cellavita HD (ADORE-HD) (Estevez-Fraga & et al., 2022) phase 2/3 trial is registered (NCT04219241—ADORE-EXT).

Strategies Targeting Neuroinflammation

Expression and accumulation of mHtt in neurons, as well as in microglia, have been implicated in microglial activation and ignition of the neuroinflammatory cascade (Lee & et al., 2019). As such, therapies trying to mitigate inflammatory responses have been developed and evaluated.

Laquinimod

Laquinimod is an orally administered small immunomodulatory molecule that shifts T helper cell (Th) polarization towards a Th2 polarization and promotes BDNF production (Brück & Wegner, 2011). It is currently used in the treatment of relapsing-remitting multiple sclerosis (Gurevich & et al., 2010) but has also been shown to reduce Bax expression and caspase-6 activation in cultured neurons (Ehrnhoefer & et al., 2016), as well as to improve striatal pathology and motor function in R6/ 2 HD mice (Ellrichmann & et al, 2017).

Drugs Targeting TNF-α

Tumor necrosis factor-α (TNF-α) is a cytokine associated with immune response, inflammation, and apoptosis (Jurcau & Ardelean, 2021, Jurcau & Simion, 2021). Increased levels of TNF-α have been found in the serum, brain tissue, and cerebrospinal fluid of HD

patients as well as of HD gene carriers (Politis & et al., 2015). The study is still in the experimental stage.

Antibody-Based Therapies

Antibody-based therapies have been evaluated in synucleinopathies and tauopathies (Jurcau & Nunkoo, 2021) and are emerging as potential therapies in genetic disorders of the central nervous system as well. VX15/2503 (pepinemab) is an IgG4 monoclonal antibody that inhibits semaphorin 4D, a protein that promotes glial cell activation and leads to oligodendrocyte and neural precursor cell apoptosis (Leonard & et al., 2015). In phase 2, a double-blinded clinical trial conducted on patients with late prodromal or early manifest HD to evaluate safety, pharmacokinetics, and pharmacodynamics (SIGNAL, NCT02481674), VX15/2503 appeared safe and even efficient in prodromal HD.

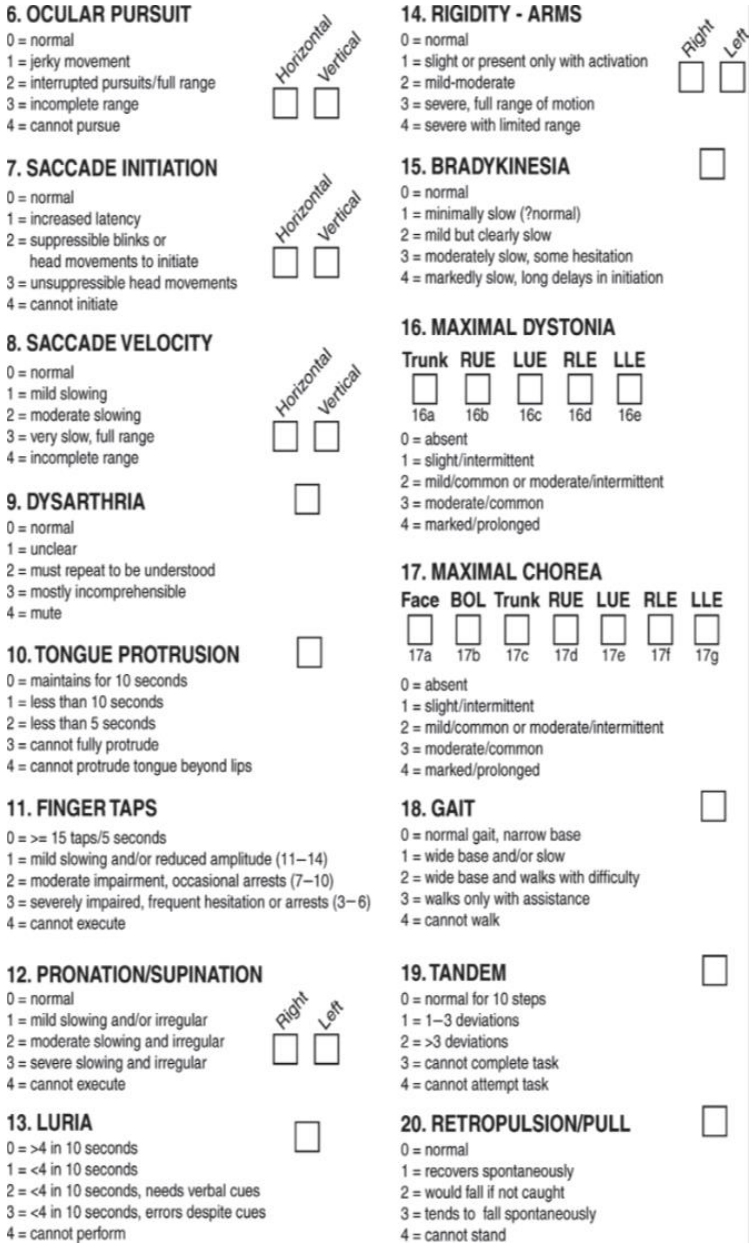

Figure. Motor subset of UHDRS (4).

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Turmeric and Its Effects On Health

Hülya TOSUN

1. Definition

Curcumin, commonly known as 'Turmeric' or the 'Golden Spice,' is a hydrophobic polyphenol derived from the rhizomes of perennial plants belonging to the ginger family (Zingiberaceae). The family comprises various species like Curcuma longa, Curcuma amada, Curcuma zedoaria, Curcuma aromatic, and Curcuma ractakanta. Curcuma longa (turmeric) is the most popular and widely cultivated species among these. Curcumin, also referred to as diferuloylmethane, constitutes the medicinal component of turmeric and is isolated from Curcuma longa (Gupta, Patchva & Aggarwal, 2013). According to a study conducted by Jiang, Ghosh, and Charcosset in 2021, the chemical formula of curcumin is stated as 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptane-3,5-dione as a diphenylheptanoid polyphenol (Jiang, Ghosh, & Charcosset, 2021). The rhizomes of Curcuma longa comprise 3-5% of three curcuminoid derivatives, which include curcumin (75%), demethoxycurcumin (10-20%), and bisdemethoxycurcumin (5%). Among these, curcumin is the most important bioactive compound (Jiang, Ghosh, & Charcosset, 2021).

Indigenous to Southeast Asia, turmeric is primarily cultivated commercially in this area, especially in India (https://www.nccih.nih.gov/health/turmeric). Curcumin, long recognized as a spice and natural colorant (food dye E100) in Indian curries, also serves as an ingredient in traditional Chinese medicines (Jiang, Ghosh, & Charcosset, 2021). It has poor solubility in water and ether but dissolves in ethanol (Shah & et al., 2020). Numerous extraction methods are used to obtain curcumin from turmeric, from conventional techniques like soxhlet extraction, maceration, and solvent extraction to advanced approaches such as ultrasound, microwave, and enzyme-assisted extraction supercritical fluid extraction (Jiang & et al., 2021). Consuming turmeric alone does not offer significant benefits due to its low bioavailability, which is attributed to poor absorption, fast metabolism, and quick elimination. However, certain ingredients can enhance turmeric's bioavailability. For instance, piperine, the primary active component in black pepper, has been found to boost bioavailability by 2000% when combined with curcumin in a complex (Hewlins & Kalman, 2017).

2. Benefits

In addition, curcumin's ability to interact with various molecular targets enables it to act as a chemopreventive agent and inhibit inflammatory cell proliferation and angiogenesis. These properties are associated with the reduction of proinflammatory cytokines, nitric oxide synthesis (iNOS) enzymes, cyclooxygenase-2 (COX-2), lipoxygenase, xanthine oxidase, and malondialdehyde (MDA) (Jakubczyk & et al., 2020; Tabanelli, Brogi, & Calderone, 2021). Research suggests that curcumin may be an effective antioxidant that minimises the effects of oxidative stress. By interacting with various molecular mechanisms, it also reduces the level of oxidative stress, which is related to its ability to chelate heavy metals or regulate the activity of numerous enzymes, among other actions (Jakubczyk & et al., 2020).

The Food and Drug Administration (FDA) has recognized curcumin as a compound generally considered safe (Jakubczyk & et al., 2020). Curcumin has numerous therapeutic properties, such as anticancer, anti-inflammatory, anti-angiogenic, immunomodulatory, and antioxidant effects in various diseases. It is known to enhance overall energy, alleviate intestinal gas, eliminate parasites, support digestion, manage menstrual bleeding, dissolve gallstones, and mitigate arthritis symptoms. In several South Asian countries, curcumin is also believed to have antibacterial properties and is utilized as an antiseptic for treating cuts, burns, and bruises (Prasad & Aggarwal, 2011). Moreover, it is considered a dietary supplement for addressing digestive disorders, respiratory infections, allergies, liver disease, and depression. Scientific research has shown that curcumin has chemotherapeutic, chemopreventive, immunomodulatory, and wound-healing properties (https://www.nccih.nih.gov/health/turmeric). According to the United States Department of Agriculture Agricultural Research Service (USDA), turmeric contains a variety of vitamins (B1, B2, B3, B4, B5, B6, B9, C, E, and K) and minerals (copper, zinc, iron, phosphorus, calcium, magnesium, manganese, potassium, selenium, and sodium) (USDA, 2020). Ahmad et al. (2020) reported that turmeric's phytochemical profile offers antioxidant, anticarcinogenic, anti-inflammatory, antimutagenic, antimicrobial, antifungal, antiviral, hypolipidemic, and neuroprotective properties, as well as protective and therapeutic effects against cardiovascular diseases. Curcumin has also been found to be a potentially beneficial additive in treating irritable bowel syndrome due to its unique antioxidant and anti-inflammatory actions and its ability to modulate the gut microbiota (Jakubczyk & et al., 2020). It demonstrates a wide range of properties related to depression pathophysiology and has been shown to exhibit antidepressant activity in various animal models and clinical trials (Ramaholimihaso, Bouazzaoui, & Kaladjian, 2020).

Furthermore, curcumin's capacity to interact with multiple molecular targets allows it to function as a chemopreventive agent and to inhibit inflammatory cell proliferation and angiogenesis. These properties are linked to the reduction of proinflammatory cytokines, nitric oxide synthesis (iNOS) enzymes, cyclooxygenase-2 (COX-2), lipoxygenase, xanthine oxidase, and malondialdehyde (MDA) (Jakubczyk & et al., 2020; Tabanelli, Brogi, & Calderone, 2021). Research indicates that curcumin may be an effective antioxidant that reduces the effects of oxidative stress. By interacting with various molecular mechanisms, it also decreases the level of oxidative stress, which is connected to its ability to chelate heavy metals or regulate the activity of numerous enzymes, among other actions (Jakubczyk & et al., 2020).

Figure 1. Turmeric, *(Curcuma Longa 2022)*

3. Disadvantages

There are some significant drawbacks to the clinical use of curcumin, including rapid metabolism, poor oral bioavailability, low water solubility, and quick systemic elimination, despite its many benefits (Dei & Ghidoni, 2019). To address these challenges, research on nano-curcumin is being conducted. In these studies, biodegradable polymer nanoparticles (nano-curcumin) improve curcumin's solubility, stability, and half-life while supporting its free radical scavenging activity (Gera & et al., 2017). Due to its bile-enhancing effect, turmeric may trigger biliary colic in people with or at risk for gallstones, so it should be avoided in this group. Furthermore, a small number of users have reported gastrointestinal side effects, such as diarrhea and nausea. However, it is essential to note that no acute or chronic toxicity has been observed, even at high doses, in animal studies (Asher & Spelman, 2013).

4. Effects on the Health of Turmeric

Use in cancers

Cancer is a prevalent disease that presents significant challenges due to its difficult and expensive treatment options worldwide. Various clinical studies on the consumption of curcumin alongside chemotherapy drugs in cancer treatment demonstrate that curcumin enhances the efficacy of chemotherapy and radiotherapy. Consequently, the patient's survival time is extended (Mansouri & et al., 2020).

Curcumin has anti-inflammatory, immunomodulatory, and wound-healing properties. Radiation-induced oral mucositis (RIOM) is the most severe non-hematological complication affecting nearly all head and neck cancer patients during radiotherapy (RT). In a study involving 74 patients with head and neck cancer requiring radiotherapy, nanoparticulate curcumin (0.1%) was compared to 0.15% benzydamine mouthwash. While neither mouthwash completely prevented the onset of RIOM, using a mouthwash containing 0.1% curcumin significantly delayed the onset of RIOM (Shah & et al., 2020).

Another study examined the impact of curcumin on treating cancer anorexia-cachexia syndrome in patients with locally advanced or advanced head and neck cancer. In this randomized controlled trial with twenty tube-fed patients, the experimental group (n=10) received oral curcumin (4000 mg daily), while the control group (n=10) received a placebo for eight weeks. The addition of turmeric resulted in a significant increase in muscle mass compared to standard dietary supplementation. It also showed improvements in other body composition parameters, hand grip strength, and a decrease in the absolute lymphocyte count. Thus, curcumin was found to be safe and tolerable for tube-fed patients with head and neck cancers (Thambamroong & et al., 2022).

Radiation dermatitis occurs in about 95% of patients receiving radiotherapy for breast cancer. In a randomized controlled study with 30 patients, the efficacy of curcumin in reducing the severity of radiation dermatitis was assessed. The results suggested that taking 6.0 g of oral curcumin daily during radiotherapy reduced the severity of radiation dermatitis in breast cancer patients (Ryan & et al., 2013).

A study involving 72 patients examined the effects of curcuminoids on serum anti-inflammatory cytokines and quality of life in colorectal cancer patients undergoing chemotherapy. Patients were divided into a curcuminoid capsule (500 mg/day) group (n = 36) and a placebo group (n = 36) for eight weeks. The findings indicated that curcuminoid supplementation for an eight-week period (500 mg/day) could improve serum levels and quality of life in stage-3 colorectal cancer patients compared to the placebo (Panahi & et al., 2021).

Antioxidant potential refers to the capacity to neutralise free oxygen radicals that are overproduced due to environmental factors. The body's defence mechanisms often need support to combat the effects of oxidative stress. Literature data suggest that curcumin has antioxidant activity, which can significantly reduce oxidative stress levels (Jakubczyk & et al., 2020).

Use in gynaecological diseases

Patients who suffer from Polycystic Ovary Syndrome (PCOS) may benefit from curcumin's many medicinal advantages. An investigation was made on how curcumin might help PCOS sufferers with their hyperandrogenism, insulin resistance, and blood sugar levels. In this study, 72 PCOS-afflicted women received either a placebo for the first 12 weeks or 500 mg of curcumin three times each day. Throughout the course of the study, no significant side effects of curcumin were noted. The findings suggested that curcumin might be a safe and practical supplement for treating PCOS-related hyperandrogenemia and hyperglycemia. However, the authors recommend further studies using different dosages for longer durations to support these findings (Heshmati & et al., 2021).

Young women frequently complain of primary dysmenorrhea and premenstrual syndrome (PMS). A study focused on how turmeric affected premenstrual symptoms and dysmenorrhea. 62 participants in the experimental group and 62 controls consisted of the study group. For three menstrual cycles, 500 mg of curcuminoid was administered to the test group seven days before and three days after menstruation. At the end of the study, it was found that premenstrual symptoms and dysmenorrhea were reduced. However, the author states that working with a larger sample will yield stronger results (Bahrami & et al., 2021). The results of another study also showed that administering a turmeric preparation helps reduce menstrual pain (dysmenorrhea) (Makiyah & Anggraini, 2023).

The effects of curcumin on vitamin D levels in young women with premenstrual syndrome and dysmenorrhea were examined in a randomised controlled trial. In this study, the experimental group received 500 mg of curcuminoid plus 5 mg of piperine seven days prior to menstruation, while the control group received a placebo. Three days after the menstrual period, the medication was stopped. It was found that curcumin supplementation significantly improved vitamin D and liver function enzyme tests in women with premenstrual syndrome and dysmenorrhea at the end of the study, which also measured serum vitamin D levels, kidney function, and liver enzymes before and after the intervention (Arabnezhad & et al., 2022).

Curcumin was found to have an effect on lowering the intensity of premenstrual symptoms in another study looking at its impact. This effect may have been mediated through the modulation of neurotransmitters and curcumin's anti-inflammatory properties (Khayat & et al., 2015).

Use in COVID 19

Coronavirus is an ongoing infectious disease worldwide. In 2020, a study was conducted investigating the effects of Nano-curcumin in modulating inflammatory cytokines in Coronavirus disease. In the study, there were 40 participants in the experimental group and 40 in the control group. Of the 40 in the experimental group, 20 received a placebo, and 20 received nano-curcumin. Using Real-time PCR and ELISA, the study assessed the mRNA expression and cytokine secretion levels of IL-1β, IL-6, TNF-a, and IL-18. As a result, nano-curcumin, a herbal remedy with anti-inflammatory properties, helped COVID-19 patients recover by reducing the rate of inflammatory cytokines, particularly IL-1β and IL-6 mRNA expression and cytokine secretion (Valizadeh & et al., 2020). Results of a subgroup analysis in another study

showed a higher benefit with the use of combination regimens and administration of curcumin within 5 days of symptom onset (Shafiee & et al., 2023).

Use in Diabetes

In a study on the efficacy of curcumin in delaying the onset of type 2 diabetes mellitus (T2DM) in a pre-diabetic population, 240 participants were given curcumin capsules for nine months. At baseline and at 3, 6, and 9 months during the intervention, changes in -cell function (homeostasis model assessment [HOMA]-, C-peptide and proinsulin/insulin), insulin resistance (HOMA-IR), an anti-inflammatory cytokine (adiponectin), and other parameters were observed. As a result, the number of pre-diabetic individuals who developed T2DM was significantly reduced. Furthermore, curcumin treatment was also shown to improve overall β-cell function with very mild side effects (Chuengsamarn et al., 2012). In a systematic review by Marton et al. (2021), it was stated that the anti-diabetic activity of curcumin might be may result from its ability to suppress oxidative stress and inflammatory process. It was also found to significantly reduce fasting blood sugar, glycosylated haemoglobin and body mass index. The nanocurcumin was also associated with substantial reductions in triglycerides, VLDL-c, total cholesterol, LDL-c, HDL-c, serum C-reactive protein and plasma malonaldehyde (Marton & et al., 2021).

Use in musculoskeletal diseases

A recent study aimed to explore the potential therapeutic benefits of turmeric for osteoarthritis treatment, and to investigate its mechanisms of action. The study involved 102 participants, with 51 participants receiving curcumin treatment and the other 51 receiving ibuprofen. The curcumin group demonstrated greater improvements in joint mobility and reduced inflammation. In vitro experiments revealed that curcumin lowered the apoptosis rate of chondrocytes and decreased the levels of inflammatory factors, while the Wnt/β-catenin inhibitor had the opposite effect. Overall, the study found that curcumin is a safe and effective option for managing the symptoms of osteoarthritis (Yuan & et al., 2022).

A comparison study was conducted to evaluate the effectiveness and safety of curcumin and diclofenac in treating knee osteoarthritis (OA). 139 patients were assigned to either receive 500 mg of curcumin or 50 mg of diclofenac. The results of the study showed that curcumin had similar effectiveness to diclofenac in treating knee OA. Moreover, curcumin was better tolerated by patients with knee OA, suggesting that it could be a viable treatment option for those who cannot tolerate the side effects of non-steroidal anti-inflammatory drugs. Another study found that curcumin was just as effective as ibuprofen in treating knee OA. Furthermore, a study on rheumatoid arthritis patients revealed that curcumin was almost as effective as phenylbutazone in reducing joint swelling and improving walking time.

A recent study examined how taking curcumin supplements impacted oxidative stress, inflammation, muscle damage, and muscle pain. Nineteen male participants were given either curcumin (1.5 g/day) or a placebo. The study found that curcumin was able to decrease muscle damage and perceived muscle soreness without negatively affecting the body's natural inflammatory response after exercising (Ms SAB & et al., 2020).

There is scientific evidence that curcumin has strong anti-inflammatory and anti-arthritic properties. People who have rheumatoid arthritis (RA) suffer from chronic inflammation and sometimes metabolic disorders, which can cause damage to the cartilage. A study was conducted to examine how curcumin affects patients with active rheumatoid arthritis. The study compared curcumin to diclofenac sodium and included 45 participants. One group was given curcumin (500 mg), while the other group received diclofenac sodium (50 mg). During the

study, a reduction in joint tenderness and swelling scores was observed. It was discovered that curcumin treatment was safe for patients with active rheumatoid arthritis and did not have any side effects (Chandran & Goel, 2012).

A randomized controlled trial was conducted to investigate the effects of curcumin supplementation on the lipid profile, metabolic parameters, and inflammatory factors in women with rheumatoid arthritis (RA). The study involved 48 women, with the experimental group receiving 500 mg of curcumin daily for eight weeks, while the control group received a placebo. The participants' physical activity levels, dietary intake, anthropometric measurements, and fasting blood samples were evaluated at the beginning and end of the study. The findings indicated that curcumin consumption could be beneficial in managing metabolic factors, inflammation, and adiposity in women with RA, suggesting that it could be incorporated into an integrated approach (Pourhabibi & et al., 2022).

A recent study delved into the effects of using curcumin ointment to alleviate knee pain in older adults with osteoarthritis. The study included 72 elderly adults who experienced knee pain as a result of osteoarthritis, and they were divided into two groups. The intervention group received curcumin 5% ointment twice daily for six weeks, while the control group received Vaseline ointment. The results of the study showed that curcumin significantly reduced the mean pain intensity in the intervention group over time. The findings suggest that applying 5% curcumin ointment topically can significantly reduce knee pain in older adults with knee osteoarthritis (Jamali, Adib & Soleimani, 2020).

Use in gastrointestinal diseases

Numerous studies have shown the beneficial effects of turmeric on digestive issues and irritable bowel syndrome. To further explore this, a study was conducted to examine the impact of Curcugen™, a curcumin extract, on gastrointestinal symptoms, mood, and quality of life in adults with digestive complaints. The study involved a randomized controlled trial where the experimental group received 500mg of Curcugen™ while the control group was given a placebo for eight weeks. As a result, a significant improvement was noted in digestive complaints and anxiety levels in the curcumin group (Lopresti & et al., 2021).

A recent study examined the impact of curcumin on reducing symptoms of dyspepsia in patients. The study also evaluated the effectiveness of famotidine treatment combined with curcumin supplementation. A total of 75 patients participated in the study, with 39 in the intervention group and 36 in the control group. The intervention group received a daily dose of 500 mg of curcumin and 40 mg of famotidine for one month, while the control group received a placebo and 40 mg of famotidine. Results showed a significant decrease in dyspepsia severity ($p < 0.001$) and H. pylori infection rate ($p = 0.004$) in the intervention group immediately after treatment and during follow-up. This study suggests that curcumin therapy may be a helpful supplement for managing functional dyspepsia symptoms and eliminating H. pylori in patients (Panahi & et al., 2021).

Use in Neurological Diseases and Depression

A study was conducted to investigate curcumin’s effect in treating depressive symptoms in individuals with major depressive disorder. Curcumin has been shown to affect various biological mechanisms associated with major depression, namely monoaminergic activity, immune-inflammatory and oxidative and nitrosative stress pathways, hypothalamic-pituitary-adrenal (HPA) axis activity, and neuro progression. A total of 56 subjects participated in the study (n=28 curcumin and n=28 placebo), and the intervention group was given 2x1,500 mg of curcumin for 8 weeks. In the study, curcumin was significantly more effective than a placebo

at improving various mood-related symptoms. At the end of the study, 4 to 8 weeks after treatment, it appeared to provide partial support for the antidepressant effects of curcumin in people with major depressive disorder (Lopresti & et al., 2014).

In some previous animal experiments, a study was conducted based on the potential antidepressant-like activity of Curcuma longa. In this designed study, the efficacy and safety of curcumin were compared with fluoxetine in patients with major depressive disorder (MDD). A six-week treatment was given to the intervention (n=30) group (curcumin 1000 mg) and fluoxetine (20 mg) to the control group. This study showed that curcumin could be used as an effective and safe treatment modality in patients with MDD without concomitant suicidal ideation or other psychotic disorders (Sanmukhani & et al., 2013). This suggests that curcumin may offer an alternative or complementary treatment option for individuals with MDD, although further research is needed to fully understand its efficacy and safety profile.

Use in Migraine

Recent research delved into the potential impact of curcumin on migraine management. The study examined the effects of supplementing obese and overweight patients with migraine with nano-curcumin, and how it affected adipokine levels and clinical manifestations. A total of 44 patients took part in the study, with the intervention group receiving a daily dose of 80mg of nano-curcumin for two months. The outcomes showed that the supplement significantly reduced headache attacks' frequency, severity, and duration. These findings suggest that curcumin could offer a fresh approach to managing migraine pain (Sedighiyan & et al., 2022).

Furthermore, another study examining the relationship between migraine and curcumin hypothesised that curcumin, possessing anti-oxidative and anti-neuroinflammatory properties, could potentially yield beneficial effects for migraine sufferers. At the end of the study, it was observed that the phytosomal formulation containing highly bioavailable curcumin (a solid dispersion preparation of curcumin with phosphatidylserine) was able to cross the blood-brain barrier, effectively reducing neuroinflammation, oxidative stress, and neurotoxicity. Consequently, it was determined that phytosomal curcumin might alleviate headaches and other migraine-associated complications, ultimately improving the quality of life for those affected by migraines (Shojaei & et al., 2023).

Memory and curcumin

A study was carried out to explore how curcumin might affect memory. The hypothesis underpinning this research posited, “Due to the anti-inflammatory properties of curcumin, which may protect the brain from neurodegeneration, it exerts an impact on memory in adults without dementia.” At the study’s conclusion, daily oral administration of “Theracurmin” was found to enhance memory and attention in adults unaffected by dementia. It was reported that brain tomography correlated with reductions in amyloid and tau deposition in brain regions responsible for mood and memory modulation. However, further research is necessary to comprehensively understand these findings (Small & et al., 2017).

Curcumin in vascular diseases

Recent studies have investigated the protective properties of curcumin in various cardiovascular diseases, including cardiac hypertrophy, heart failure, drug-induced cardiotoxicity, myocardial infarction, atherosclerosis, abdominal aortic aneurysm, stroke, and diabetic cardiovascular complications. Turmeric has been found to delay cellular senescence, which reduces ageing-related oxidative stress and vascular dysfunction. In one study, aged mice were supplemented with curcumin for four weeks, resulting in improved vasodilation and

reduced age-related great artery stiffness. These effects are due to the restoration of nitric oxide bioavailability, the reduction of vascular superoxide production and oxidative stress, and the reduction of Collagen I deposition (Fleenor & et al. 2013).

Curcumin intake has been positively correlated with improved arterial hemodynamics and reduced endothelial dysfunction in postmenopausal women at risk of cardiovascular disease. Additionally, curcumin supplementation in healthy middle-aged and older adults was associated with a significant improvement in vascular endothelial function. Studies have also shown that curcumin positively affects glycemic status and insulin sensitivity, promotes the beige of white adipocytes, and reduces obesity-associated adipose tissue inflammation. These findings suggest that curcumin may have therapeutic potential in the treatment of obesity-causing cardiovascular diseases (Cox & et al. 2022).

Early studies in rabbits on an atherogenic diet revealed that turmeric extract reduced the development of atherosclerosis (Quiles & et al. 2002). In another experiment, curcumin was found to reduce the size of atherosclerotic lesions in a series of mouse models for atherosclerosis (Hasan & et al. 2014). This is attributable to its ability to change LDL to HDL (Cox & et al. 2022).

Regarding remodelling processes after myocardial infarction (MI), curcumin has been shown to inhibit the regulation of expression of various collagens, collagen deposition, overactivation of matrix metalloproteinases, and persistence of numerous myofibroblasts. Thus, it positively affects remodelling and effectively reduces the size of the scar. In line with these findings, curcumin also alleviates the disorders in cardiac functions after MI. These studies show that curcumin can effectively prevent maladaptive cardiac repair and preserve cardiac function after MI (Cox et al. 2022; Liao et al. 2021).

A study was conducted on healthy middle-aged and older adults to test the hypothesis that curcumin would enhance vascular resistance, improve conduit artery endothelial function, and reduce great elastic artery stiffness. Thirty-nine participants were randomly assigned to receive either 12 weeks of curcumin supplementation (2000 mg/day Longvida®; n=20) or a placebo (n=19). At the study's conclusion, it was found that 12 weeks of curcumin supplementation improved resistant artery endothelial function by increasing vascular nitric oxide bioavailability and reducing oxidative stress, as well as enhancing conduit artery endothelial function (Santos-Parker & et al., 2017).

Use in oral lichen planus

Oral lichen planus (OLP) is an autoimmune disease affecting the mucocutaneous T cells. For treating OLP, corticosteroids are commonly used as a first choice, but their side effects have led to the exploration of alternative therapies. This study evaluated the therapeutic effect of oral Nano-Curcumin, which has better bioavailability than regular curcumin. Sixty patients were split into two groups: the curcumin group received 'Nano-Curcumin 80 mg' and the control group received 'Prednisolone 10 mg' treatment for one month. The results showed that oral curcumin reduced pain and lesion size and could be used as an alternative therapy for patients who cannot take corticosteroids, but with caution. The authors provided important advice, stating, "The amount of curcumin dose is more important than the duration of use in the improvement of oral lichen planus" (Kia & et al., 2020).

5. Conclusion

In this study, the definition of turmeric, its benefits and risks, and academic research have been examined. Curcumin is a beneficial plant that continues to be deeply researched due to its anticancer, anti-inflammatory, anti-angiogenic, immunomodulatory, antioxidant, and

antidepressant properties in various diseases. Not every source of information about turmeric is accurate. Therefore, this natural wonder, which has potent effects, should not be used without a specialist's recommendation. The study highlights that the effects of turmeric on health warrant further research.

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Importance of Perinatology Examination: Corpus Callosum Anomalies with Normal Karyotyp A Remarkable Case

Sadun SUCU[1]

Introductıon

The greatest white matter interhemispheric tract bridging the brain hemispheres is the corpus callosum.(Edwards et al., 2014) The functional integration of sensory, motor, visuomotor, and cognitive processes (language, abstract thought, and the integration of complex sensory information) depends on these relationships.(Edwards et al., 2014; Palmer & Mowat, 2014) Among the illnesses or developmental anomalies of the corpus callosum are: complete agenesis, partial agenesis (hypogenesis) thinning (hypoplasia), thickening (hyperplasia). Agenesis of the corpus callosum (ACC) is a heterogeneous disorder caused by impairment of a number of embryonic processes, including commissural axon control, neuronal specification, and midline telencephalic patterning. The disturbance may have a genetic, viral (such as the TORCH virus or Zika virus), vascular, or toxic (such as fetal alcohol syndrome) etiology.(Edwards et al., 2014) The prevalence of ACC has been estimated to be 1:4000–1:5000 live births, however patients with neurodevelopmental impairments have been shown to have rates of 2–3%.(Paul et al., 2007; Sotiriadis & Makrydimas, 2012)

Case

The case involves a 37-year-old woman of African descent at 23 weeks' gestation. There is no consanguinity between the patient and her husband. There is no known disease in her past medical history or known genetic diseases in her family history. She is a patient who has no active medical conditions and comes for routine outpatient examination. The prenatal screening test has no higher risk than the population her age. Nevertheless, invasive genetic diagnostic testing was recommended for the patient because the age risk was 1:165. Amniocentesis was scheduled for the patient when chorionic villus sampling (CVS), which was performed due to advanced maternal age, was insufficient for the first rapid result and the final CVS result was 46,XY(8),46, XX (15). The rapid result of the amniocentesis performed was evaluated as insufficient, because a sufficient informative marker of the 18th chromosome could not be obtained, and the final result of the amniocentesis was awaited. As a result of the final amniocentesis, no structural or numerical chromosomal anomaly was found. Although the constitutional genetic scan of the patient was normal, many fetal anomalies were detected in the ultrasonography performed in the perinatology clinic. No cavum septum pellcidum was seen in the transverse neurosonogram of the fetus. However, a trilaminar midline echo and ventriculomegaly (colpocephaly) were noted. Hypoplasia of the cerebellar vermis and DandyWalker spectrum were suspected due to posterior fossa abnormality. In the sagittal neurosonogram section, corpus callosum and pericallosal artery were not observed. Increased subarachnoid distance and abnormal brain sulcus development were seen. Fetal face was dysmorphic. An inlet ventricular septal defect was seen in the fetal heart and the stomach was small. (oesophageal atresia) The umbilical vein was opening directly to the heart (right atrium). This abnormal vascular access made us think of agenesis of the ductus venosus. Renal pelvis

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was wide in both fetal kidneys. (pyelectasis) The pregnancy of the patient was terminated with fetocide procedure due to multiple anomaly at 23rd gestational week. Upon the recommendation of the geneticist, it was planned to study microarray from the abortion material after termination.

Discussion

Corpus callosum (commonly referred to as the "rostrum", "the body", or "the splenium") is the hypoechoic area of the brain between the inferior part of the cavity (the Cavum Septi Pellucidi) and the superior part (the Cingulate Gyrus). Pericallosal Artery is imaged higher than the Corpus Callosum with color Doppler imaging.(Edwards et al., 2014) For this structure, which can be evaluated, it is necessary to be alert in routine scans. The two most significant signs that the callosal abnormality needs to be further evaluated are: nonvisualization of cavum spermaticum (cavum septi pellecolucidi) and ventricular (lateral) size >10 mm. In a study using both ultrasound and magnetic resonance imaging (MRI), 13 percent of fetal abnormalities of the callosal callosum were identified in the 20 to 22 week gestational age range for fetal anomalies. Only 24 percent of fetal abnormalities were isolated in the study (callosal dysgenesis). The remainder had a CNS, karyotype, or other major abnormality.(Li et al., 2012) The prognosis of individuals with disorders of the callosum depends on the presence or absence of related abnormalities and genetic disorders. Identifying the cause and/or related abnormalities may lead to better counseling of the pregnant patient about the long-term prognosis of the baby. However, a systematic review found that even in isolated agenesis, the frequency, type, and degree of impairment (if any) are difficult to predict because of the wide variability in outcome measures used in available studies, duration of care, and neurodevelopmental tools.(D'Antonio et al., 2016) In our presentation and in light of current literature information, the importance of abnormalities of the corpus callosum is emphasized and we note that abnormalities of the corpus callosum are not easily detected and detailed ultrasonography is of considerable importance in addition to standard genetic screening tests. We believe that ultrasonography is the main element in the detection of fetal anomalies for which standard genetic testing is often inadequate and detailed, expensive advanced genetic testing (microarray etc.) may be required to make a diagnosis.

Result

It is very challenging to counsel patients with ACC due to study design, selection bias, absence of a control group, and different definition and imaging protocols. In the context of the case presented, the importance of perinatological examination in every patient is demonstrated and the value of detailed ultrasonography in addition to the usual prenatal biochemical examinations is emphasized.

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A Concise Review Of Active Breathing Control (ABC) System For Respiratory Motion Management In Non Small Cell Lung Cancer (NSCLC) Radiotherapy (RT)

Yelda ELCIM

Introduction

Respiratory motion management comprises a critical aspect of successful radiotherapy (RT) applications for thoracoabdominal tumors. While accuracy and precision of RT is continuously increasing with respect to advances in technology, normal tissue sparing has been an indispensable aspect of current RT practice. Thoracoabdominal tumors comprise a critical part of clinical RT applications, and optimal management of respiratory motion is important for RT for these tumors.

The problems caused by respiratory movement during RT can be examined under 3 main headings [1]:

1. Limitations on imaging: Respiratory motion may cause motion artifacts and blurring in acquired computed tomography (CT) simulation images for RT planning. This may consequently lead to inaccuracies in target volume and critical organ delineation.

2. Limitations in treatment planning: In RT practice, an internal margin (IM) is typically used to account for respiratory motion in treatment of thoracoabdominal tumors. Since the range of respiratory motion may be high, large internal margins may be required around the target. This may lead to excessive exposure of surrounding normal tissues which may result in severe treatment related toxicity. Also, higher doses to critical organs may preclude dose escalation and hamper clinical outcomes of RT in some circumstances. Elimination of internal margins by successful respiratory motion management may enhance normal tissue sparing and allow for dose escalation which may lead to improved therapeutic outcomes.

3. Limitations in delivery of RT: The presence of intra-fractional motion during RT causes averaging and blurring along the direction of motion of dose distribution and the presence of movement between fractions causes a shift in dose distribution. This displacement causes a deviation between the intended and delivered dose distribution which may result in treatment failure.

Various techniques including motion encompassing techniques, respiratory gated techniques, forced shallow breathing techniques, breathing synchronized techniques and breath-holding techniques have been utilized to account for respiratory motion in thoracoabdominal RT [1]. Among these techniques, breath holding during treatment simulation and RT delivery deserves utmost attention. Breath holding techniques may be categorized as voluntary breath holding, breath holding at deep or moderate-deep inspiration, breath-holding without respiratory monitoring, self-breath-holding with respiratory monitoring, and breath holding with ABC system.

ABC System

ABC (Active Breathing Coordinator™, Elekta) system has been developed by Wong et al. to facilitate reproducible breath holding [2]. The ABC system is used at a pre-defined threshold, where the patient-specific breathing phase is followed, usually by controlling breath-hold during moderate or deep inspiration. The system works with a digital spirometer that measures the respiratory movement and a balloon valve connected to it. In the ABC technique, the patient breathes through the mouthpiece in free breathing. The RT technician activates the system in the respiratory cycle phase and lung volume determined before the treatment of the patient and the balloon valve closes. The patient is taught to reach the determined threshold lung volume after a few preparatory free breaths. The valve is inflated with the air compressor for a predetermined time, thus allowing the patient to hold the breath. Figure 1 shows the patient's free breathing cycle and Figure 2 shows the breath-holding phase in medium-deep inspiration.

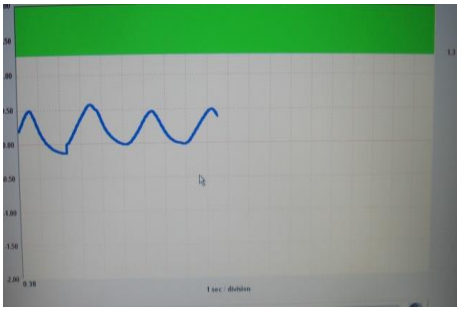

Figure 1. Free breathing cycle

Figure 2. Breath-holding phase

The breath-hold time is usually 15-30 seconds and this time completely depends on the individual performance of the patient. After a short rest, the patient should be able to stand for a period of time so that she can hold her breath again. As much as possible, one should hold one breath at each treatment angle. 75% of the maximum inspiratory volume is accepted as the breath-hold level in moderate-deep inspiration.

Immobilization of patients with a fixed and reproducible position is important in the management of respiratory motion. Using an immobilization tool will reduce set-up error and treatment uncertainty. By simulating CT (Computerized Tomography) using the ABC system and delivering the treatment under the same conditions, the target volume is assumed to be "frozen" in the stationary phase and internal margin (IM) is minimized or eliminated. This may allow for dose escalation and improved therapeutic outcomes.

Utility of ABC system for respiratory motion management in NSCLC

We have reported the utility of ABC guided RT for NSCLC with detailed dosimetric analysis [3]. Effect of Active Breathing Control-moderate deep inspiration breath-hold (ABC-mDIBH) on tumor motion and critical organ doses has been assessed in a series of 23 patients with locally advanced NSCLC. Individual tumor motion of patients with and without ABC-mDIBH was documented and comparatively analyzed. As the outcome, incorporation of ABC-mDIBH in NSCLC management resulted in statistically significant improvement in physical lung parameters of V20 (lung volume receiving ≥ 20 Gy) and mean lung dose (MLD) which are predictors of radiation pneumonitis ($p<0.001$). Also, reduction in spinal cord dose and tumor motion with ABC-mDIBH has been found to be statistically significant ($p<0.001$). Within this context, it was concluded that ABC-mDIBH increased normal lung tissue sparing in definitive NSCLC RT through improving physical lung parameters along with spinal cord dose reduction by excellent tumor immobilization. The authors reported that incorporation of ABC-mDIBH

into NSCLC RT could offer implications for potential margin reduction and dose escalation to improve treatment outcomes further [3].

Also, other studies have addressed ABC guided RT for NSCLC. Panakis et al. evaluated definition of margins in radical RT of NSCLC with ABC and the effect on physical lung parameters [4]. They determined the IM and set-up error with ABC and the effect on physical lung parameters compared to standard margins used with free breathing. They also assessed interfraction esophageal movement to determine a planning organ at risk volume (PRV). Two sequential studies have been performed using ABC in NSCLC patients who were suitable for radical RT. ABC-mDIBH was tolerated in 25 out of 30 patients (83%). The random contribution of periodic tumor motion was reduced by 90% in the y direction with ABC compared to free-breathing. The magnitude of motion reduction has been found to be less in the x and z direction. Combining the systematic and random set-up error in quadrature with the systematic and random intrafraction and interfraction tumor variations with ABC resulted in a PTV margin of 8.3 mm in the x direction, 12.0 mm in the y direction and 9.8 mm in the z direction. There was a relative mean reduction in MLD, lung V20 and V13 of 25%, 21% and 18% with the ABC PTV compared to a free-breathing PTV. The authors concluded that the reduction in PTV size with ABC resulted in an 18-25% relative reduction in physical lung parameters and PTV margin reduction had the potential to spare normal lung tissue which could allow dose-escalation if combined with IGRT [4].

McNair et al. assessed the feasibility of using ABC in patients receiving radical RT for NSCLC [5]. Eighteen patients were included, and a training session was conducted to establish the patient's breath hold level and breath hold time individually. Reproducibility of breath hold was evaluated by comparing lung volumes measured from the planning scans and the volume recorded by ABC. Patients were treated with a 3-field coplanar beam arrangement and treatment time (patient on and off the bed) and number of breath holds were recorded. The tolerability of the device was also assessed by use of a weekly questionnaire. Seventeen out of the total 18 patients completed 32 fractions of RT using ABC. All patients tolerated a maximum breath hold time >15 seconds. The mean patient training time was 13.8 minutes and no patient found the ABC very uncomfortable. Six to thirteen breath holds of 10-14 seconds were required per session. The mean treatment time was 15.8 minutes. The authors concluded that the use of ABC in patients receiving radical RT for NSCLC was feasible. A minimum tolerated breath hold time of 15 seconds was suggested before commencing treatment [5].

Brock et al. assessed feasibility and reproducibility of ABC system usage throughout radical RT for NSCLC and compared lung dosimetric parameters between free-breathing and ABC plans [6]. Treatment (64 Gy in 32 fractions, 5 days/week) was delivered by incorporation of ABC system for breath holding. The authors reported that **c**linically significant movements of GTV were seen during RT for NSCLC using ABC and image guidance was suggested with ABC. The authors concluded that the use of ABC could reduce dose volume parameters predictive for pulmonary toxicity, and could allow for equitoxic RT dose escalation [6].

Conclusion

Respiratory movement of tumors and organs in the thoracic region may lead to inaccuracies in target definition, treatment planning and delivery, along with discordance between planned and delivered dose distributions. Difficulties in precise characterization of individual tumor and organ motility may pose a major obstacle to administration of RT. This situation may become even more critical in the setting of hypofractionated regimens or Stereotactic Body Radiotherapy, where high fraction doses are delivered in a limited number of fractions. For this reason, it is a necessity to deal with breathing induced movement for radiotherapeutic management of NSCLC. While definition of small internal margins without

respiratory motion management may cause geographic miss and resultant treatment failures, definition of large IM to account for respiratory motion may increase treatment morbidity and preclude delivery of curative intent RT due to violation of critical organ dose constraints.

ABC system offers a viable method of respiratory motion management for NSCLC RT as addressed in several studies [1-6]. Reduction in critical organ doses by elimination or minimization of internal margins by use of ABC system may allow for dose escalated RT which may improve tumor control probability and treatment outcomes. Clearly, further studies are needed to assess the utility of ABC system for radiotherapeutic management of NSCLC.

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Bronchiectasis

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Description and History

Bronchiectasis, first described by Leannec in 1819, is an abnormal and permanent enlargement of one or more bronchi as a result of the destruction of the muscular and elastic components of the bronchial walls. Expansion of the bronchi may lead to inadequate mucus clearance and an increased risk of infection (Chalmers et al., 2018a). Although bronchiectasis is still considered an "orphan disease", its prevalence is estimated to be 53-566 per 100,000 and is increasing in older age and female gender (Polverino et al., 2017). It is thought that the prevalence of tuberculosis has decreased with the widespread use of antibiotics, vaccination practices, and the decrease in tuberculosis in developed countries, but it still maintains its importance in countries with inadequate basic health services and vaccination activities.

There are guidelines for the diagnosis and treatment management of patients with bronchiectasis. These are BTS in 2010, SEPAR in 2008, and ERS in 2017. For children and adolescents, there is the ERS 2021 guideline.

In bronchiectasis, bronchial dilatation is seen in medium-diameter bronchi, but may also be found in distal bronchi and bronchioles. Although gender ratios may vary according to the underlying causes, in general, the ratio of male and female gender is equal in patients with bronchiectasis (Zhou et al., 2023). Although it is mostly unilateral, it is bilateral in 30% of cases. The basal segments of the lower lobes, which are more difficult to drain than the other lobes, the lingula, and the middle lobe are frequently involved. Bronchiectasis in the left lower lobe is 3 times more common because the right main bronchus drains more easily, the left main bronchus is narrower and the left main bronchus is slightly compressed where it crosses the left main pulmonary artery.

Etiology: The etiology of bronchiectasis patients presenting clinically with productive cough and exertional dyspnea is complex and hereditary mucociliary defects, airway obstruction, immunodeficiency, and previous respiratory tract infections play a role in the etiology. (Imam & Duarte, 2020; Pasteur et al., 2000) (Table-1). In studies on the etiology of bronchiectasis, it has been reported that bronchiectasis is most frequently idiopathic, but most frequently secondary to previous infection among the known causes (Anwar et al., 2013). Especially in the management of bronchiectasis secondary to previous infections, a multidisciplinary approach should be adopted and the most appropriate treatment should be applied before the disease prognosis worsens. Although the etiology is complex, there are 2 formation mechanisms:

1-Mechanism of bronchial obstruction: Due to obstruction, atelectasis, weakening of the parenchymal tissue, and accumulation of excess and dark secretions in the bronchi occur beyond the obstructed bronchus. Resorption of parenchymal air in this bronchial area causes an increase in the elastic recoil pressure. This pressure acts on the bronchial wall and dilates the

bronchi. The secretion accumulated in the bronchus will also increase the intraluminal pressure. In addition, expiratory effort against increased airway resistance will also increase the intraluminal pressure and this will also play a role in dilatation. Expansion caused by such mechanical forces will facilitate secretion accumulation.

2-Mechanism of infection formation: The secretion accumulated in the obstructed bronchus due to impaired drainage will eventually become infected and this infection will eventually lead to destruction of the bronchial wall and a permanent bronchial enlargement. Factors predisposing to bronchiectasis and specific agents/diseases are shown in Table 1.

Table 1- Factors predisposing to bronchiectasis

Categories	Specific antities
Bronchopulmonary Infections	
Childhood infections	Measles, whooping cough
Other bacterial infections	S.aureus, Klebsiella, M.tuberculosis, H.Influenza infections
Other viral infections	Adenovirus (especially type 21), influenza, H.simplex, viral bronchiolitis
Unclassified infections	Mycotic and mycoplasmal infections
Bronchial Obstruction	
Foreign body aspiration	
Neoplasms	Adenomas, bronchogenic carcinoma
Hilar adenopathy	Tuberculosis, histoplasmosis
Mucoid plug	Allergic bronchopulmonary aspergillosis, postoperative mucoid plug
COPD	Chronic bronchitis, asthma
Acquired tracheobronchial disease	Amyloidosis, recurrent polychondritis
Congenital Anatomical Defects	
Tracheobronchial	Bronchomalacia (Williams-Campbell syndrome, tracheobronchomegaly (Mounier-Kuhn syndrome), tracheoesophageal fistula
Vascular	intralobar pulmonary sequestration, pulmonary artery aneurysm
Lymphatic	Yellow nail syndrome
Immune Deficiency Conditions	
Ig G deficiency	
Ig A deficiency	
Hereditary Anomalies	
Ciliary defects	Immotile cilia syndrome, Kartagener syndrome
α -1 Antitrypsin deficiency	
Cystic fibrosis (mucoviscidosis)	

One of the most important predisposing factors for bronchiectasis is childhood viral and bacterial infections. Chronic inflammation and infection cause deterioration in bronchial walls and mucociliary activity, and with the accumulation of secretions, the lungs become a favorable environment for the growth of bacteria, leading to recurrent infection and inflammation in a vicious cycle. (Ilowite et al., 2008; Moulton & Barker, 2012). Dense viscous secretion obstructs the airways and impaired gas exchange mechanism due to chronic inflammation results in decreased respiratory function, respiratory and peripheral muscle strength, and functional capacity. (Ozalp et al., 2012).

Factors that facilitate the formation of bronchiectasis in children are low bronchial wall resistance, narrower bronchi, incomplete development of pores, more difficult collateral ventilation, and collapse of the lung. Necrotizing pneumonias following whooping cough and measles, which are among the infectious agents in children, also cause bronchial damage. In these patients, thick sputum may cause bronchiectasis by obstructing small bronchi. Therefore, if a progressive cough with phlegm persists despite treatment of whooping cough, measles, and tuberculosis in children, the diagnosis of bronchiectasis should be considered. In patients with more than 6 weeks of recurrent acute respiratory tract infections, especially in patients with mucopurulent cough with sputum that increases in the morning, the possibility of bronchiectasis is very high**.** (*Yenigün and Kayı Cangır - 2012 - BRONCHIECTASIS IN CHILDHOOD.pdf*, n.y.)**.**

Pathogenesis in bronchiectasis due to viral agents; the virus enters the epithelial cells and secretes inflammatory mediators; increases vascular permeability through mediators, stimulates cholinergic nerves; leads to mucus production and nasal discharge. The cellular damage and ciliary destruction occur (https://dergipark.org.tr/tr/download/article-(https://dergipark.org.tr/tr/download/article-768513.pdf, n.d.). Ciliary function and mucociliary clearance are known to be the primary defense mechanisms of the lung. Foreign body, neoplasm, hilar lymphadenopathy, hilar lymphadenopathy, and mucoid plug are the factors that predispose to bronchiectasis by bronchial obstruction. In tuberculosis, cicatricial bronchiectasis occurs due to fibrotic sequelae.

Allergic bronchopulmonary aspergillosis (ABPA) is caused by a hypersensitivity reaction to Aspergillus fumigatus antigens colonizing the airways. Type I hypersensitivity reaction to Aspergillus species develops and bronchospasm occurs. The antigen-antibody complex formed by fungi at the site of mucous plugs leads to a type 3 hypersensitivity reaction. This results in bronchial destruction and proximal bronchiectasis. It usually occurs in patients with severe asthma and cystic fibrosis in the 3-5th decade of life. (Bhankhur et al., 2019; Jack & Bajaj, 2023; Vitte et al., 2017).

Williams-Champbell syndrome is a rare cause of congenital non-cystic fibrosis bronchiectasis. Anatomically, there is usually an absence or dysfunction of one or more cartilages in the fourth to sixth segment of the bronchial tree. For the diagnosis, bronchography is typical for bronchial dilatation on inspiration and collapse of almost the entire bronchial tree from the second to the sixth branch on expiration, and other causes of bronchiectasis must be excluded (Noriega Aldave & William Saliski, 2014; Williams & Campbell, 1960). Clinically, it is characterized by a persistent cough, sputum, recurrent lung infections, and clubbing.

Tracheobronchomegaly-Mounier Kuhn syndrome; first described in 1937, the main feature of this syndrome is an enlarged trachea and main bronchi, usually congenital. In 1988, the first visualizations of MKS on computed tomography (CT) were described (Krustins, 2016; *Mounier-Kuhn: Dilatation de la trachea; constatations - Google Scholar*, n.d.). Both membranous and cartilage tissue are affected. It is characterized by marked dilatation of the trachea and large bronchi, bilateral saccular bronchiectasis, and recurrent lung infections.

Intralobar sequestration; It is a separate segment of lung tissue adjacent to normal lung tissue, surrounded by visceral pleura, blooded by an abnormal artery originating from the aorta or its branches. Venous drainage is to the pulmonary vein. It is more common in the left lower lobe. More than half of the intralobar sequestrations are found in the posterior basal segment of the left lower lobe (Chakraborty et al., 2023). When infected, it causes bronchiectasis-like symptoms.

"Yellow-nail syndrome (YNS*) is* a rare condition defined by the presence of two of the three criteria: (1) slow-growing, hard, yellow and dystrophic nails, (2) lymphoedema, and (3)

respiratory disease. The first case was reported by Heller in 1927. Pulmonary involvement, especially pleural effusion, was added to the diagnostic criteria in 1966. It is an acquired disease usually affecting adults over 50 years of age (Cheslock & Harrington, 2023).

Immunodeficiency conditions causing bronchiectasis are mostly associated with humoral immunity defects. IgG deficiency is most commonly seen. Sometimes subgroup deficiency (lgG2-3-4) may be seen while IgG is normal. (Zea-Vera et al., 2022).

Primary ciliary dyskinesia (PCD) is a rare genetic disorder with structural and/or functional abnormalities in the cilia of various organs and the sperm flagella. (*Kartagener: Zur pathogenese der bronchiektasien - Google Scholar*, n.d.). Although Kartagener syndrome was previously recognized as a classic type of PCD with a triad of situs inversus, chronic sinusitis, and bronchiectasis, situs inversus is observed in half of patients with PCD (Goutaki et al., 2016; Kennedy et al., 2007). This syndrome is seen in 1.5% of patients with bronchiectasis.

a-1 antitrypsin deficiency (AATD), a major serum protease inhibitor; usually causes panlobular emphysema, there is no evidence that it causes bronchiectasis, but it is thought that AAT deficiency, and thus a lack of its anti-inflammatory properties, may cause inflammation in the bronchial wall, eventually resulting in bronchiectasis (*Araujo: Association between alpha 1 antitrypsin and...- Google Scholar*, n.d.). Data on the relationship between bronchiectasis and AATD are contradictory. Some studies have reported that the severity of AATD correlates with the severity of bronchiectasis (*Araujo: Association between alpha 1 antitrypsin and... - Google Scholar*, n.d.; Parr et al., 2007). However, there are also reports that AATD and bronchiectasis are not associated (Cuvelier et al., 2000; Pasteur et al., 2000).

Cystic Fibrosis; Hereditary autosomal recessive disease, chronic pulmonary disease, and pancreatic insufficiency due to mutations in the CFTR gene on chromosome 7 is the major organic dysfunction (Jia & Taylor-Cousar, 2023). Due to widespread exocrine gland dysfunction, the viscosity of tracheobronchial mucus increases, ciliary movements decrease and accumulated secretions obstruct the airways, facilitating bacterial settlement and causing bronchiectasis. (*Hoegger: Impaired mucus detachment disrupts mucociliary...* - , n.d.).

Young's Syndrome; In this syndrome, which is predisposing to bronchiectasis and seen in male patients, obstructive azoospermia and chronic sinopulmonary infections are present. (Lau & Lieberman, 1986). Testicular function is normal but the epididymis is covered with an amorphous material. Bronchiectasis is seen in 30-40% of cases. It is differentiated from immotile cilia syndrome by the absence of ultrastructural abnormality and from cystic fibrosis by the normal sweat test. (*Measurement of nasal potential difference in adult cystic fibrosis, Young's syndrome, and bronchiectasis. | Thorax*, n.d.).

Pathophysiology: The pathophysiology of bronchiectasis is complex due to the variety of factors involved in the etiology and the vicious circle. This is probably due to different aetiologies in different countries. In patients with bronchiectasis, due to its complex mechanism, it is very important to first determine the etiology to guide treatment (Chalmers et al., 2018b).

The main problem with bronchiectasis;

- Recurrent infection
- Inflammation
- Mucociliary clearance disorder
- The vicious circle of structural lung damage needs to be broken.

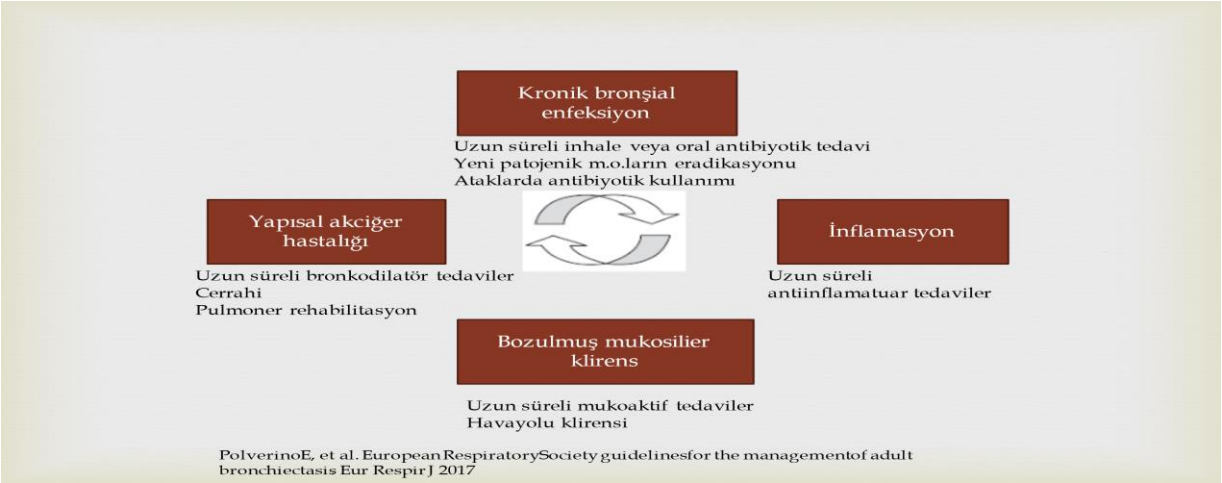

Figure 1: Pathophysiological cycle in bronchiectasis- Polverino E, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J 2017

In order to break the cycle shown in Figure 1, it is recommended that patients with bronchiectasis should be followed up by adopting a multidisciplinary approach of the following branches.

- Chest diseases
- Microbiology
- Physiotherapy
- Thoracic surgery
- 1st step health services
- Methodology

Mucociliary transport is affected by various causes of bronchiectasis. These are; 1-loss of normal ciliary epithelium 2-hereditary ciliary defects 3-abnormal composition of respiratory mucus.

Cilia are found in epithelial cells lining the respiratory tract, paranasal sinuses, middle ear, and reproductive system in many parts of the body (A & Tw, 2021; Kapania et al., 2023). In primary ciliary dysfunction, mutations causing cilia abnormal in structure and function can cause dynein arm defects and central microtubular abnormalities. Abnormal ciliary movements in the respiratory tract lead to impaired mucociliary clearance, which in turn causes chronic auto-sinopulmonary infections (Hornef et al., 2006; Knowles et al., 2013; Mirra et al., 2017).

The cause of hemodynamic disturbances in bronchiectasis is left-to-right shunting due to anastomoses between bronchial and pulmonary arterial circulation at the precapillary level.

Bronchiectasis may be focal or diffuse; focal bronchiectasis occurs after foreign body aspiration, adenopathy, benign tumor, or mucous plugs, especially in children. Bronchiectasis is uncommon in malignant tumors because the disease progression is too rapid to allow bronchiectasis to develop or the tumor has been successfully treated. Diffuse bronchiectasis may develop following aspiration of gastric contents, diffuse inflammation after harmful inhalation injury, intravenous drug intake.

Bronchiectasis anatomopathological;

1.True bronchiectasis: It is bronchial enlargement that develops with chronic infections in the bronchus and surrounding lung area as a result of weakness in the bronchial wall, chronic infection, and inadequate drainage.

2- Pseudo bronchiectasis: transient bronchial dilatations that do not cause damage to the bronchial wall, which appear due to bronchial obstruction during pulmonary infections such as atypical pneumonia and disappear following the recovery of the disease or up to 3-4 months later. (Barker & Brody, 2015).

Classification; The anatomical classification made by Reid in 1950 is the most commonly used and correlates pathological findings with radiological findings. According to this classification;

1-Cylindrical bronchiectasis; bronchographic bronchography does not show the progressive narrowing of the bronchi normally seen. There is minimal dilatation in the bronchi. Bronchi terminate abruptly and square on the bronchogram. Because the walls of the airways are oedematous and obstructed with mucus plugs, the smaller bronchi are not filled with radiopaque material and are not seen on the bronchogram.

2-Varicous bronchiectasis; the appearance of the bronchus is irregular. This irregularity is formed by stenosis and dilatation in places that distort the shape of the airways. The shape of the bronchus resembles varicose veins and the stenosis and dilatation in places may give the appearance of "lined up rosary beads".

3-Saccular or cystic bronchiectasis; bronchi have become cystic structures filled with pus. These structures look like grape clusters (Marostica & Fischer, 2006). The dilatation increases towards the lung periphery and the bronchi terminate in balloon-shaped cavities.

Clinic: The most common finding is chronic cough and mucopurulent expectoration. Although complaints usually increase in winter, they may persist throughout the year. In over 80% of cases, cough and expectoration and recurrent pneumonia following URTI since childhood are present. When 24-hour sputum is collected in a container, it forms a layer of pus, cell debris, fibrin, elastic fibers at the bottom, a serous layer in the middle, and 3 layers of colorless or slightly green-colored sputum containing foamy, mucus, and pus at the top. Hemoptysis is a complication ranging from chronic small volumes to massive hemoptysis, which can be life-threatening. Hemoptysis is usually due to chronic airway inflammation and infection, but can also be massive hemoptysis due to the rupture of a tortuous blood vessel (Osaki et al., 2000). Bronchiectasis is a common etiology in patients presenting with hemoptysis (Choi et al., 2018; King et al., 2006; Seitz et al., 2010). In a cohort of bronchiectasis patients in France, 20% of patients had a history of hemoptysis (Aksamit et al., 2017). Bronchiectasis developing as a sequela of tuberculosis may present only with hemoptysis. Hemoptysis is mostly caused by anastomoses between bronchial arteries and pulmonary vessels and bronchial artery aneurysms. Other symptoms may be absent because drainage is easy due to gravity.

Dyspnea and cor pulmonale may develop in patients with extensive bronchiectasis. In this case, signs of right heart failure are detected.

Physical Examination: Some patients are found normal. In the diseased areas, coarse rales starting in early inspiratory and continuing in expiratory are characteristic. Clubbing decreases from 40% to 7%. Nasal polyps, rhinitis, sinusitis, wheezing, cyanosis, and cor pulmonale findings may be found.

Laboratory: Minimum aetiological tests in adults with a new diagnosis of bronchiectasis;

1) WBC

2) Serum immunoglobulins (IgG, IgA, and IgM);

3) Testing for allergic bronchopulmonary aspergillosis (ABPA or in patients with severe or rapidly progressing disease).

Neutropenia/lymphopenia in complete blood count may be significant in terms of primary-secondary immunodeficiency and lymphocytosis/hematological malignancy may be significant in terms of secondary immunodeficiency.

In terms of ABPA; Total serum Ig E, Aspergillus specific Ig E, Aspergillus specific Ig G, and Aspergillus skin test should be requested.

If radiological features suggest non-tuberculosis mycobacterium (NTM), weight loss, hemoptysis, rapid clinical deterioration, symptoms unresponsive to standard treatment; sputum culture/mycobacteria culture or single bronchoalveolar lavage should be checked for 3 consecutive days. (Polverino et al., 2017).

Radiology: Although none of them are definitive findings on chest radiography, increase in markings, thin parallel lines called tram track appearance, tubular shadows, volume loss especially in the lower lobes, displacement of fissures, heart, trachea, and mediastinum, crowding of vascular shadows, very slowly resorbing bronchopneumonia foci, honeycomb appearance, and air-fluid level in some of the sacs in saccular bronchiectasis can be seen. While bronchography was a diagnostic method that was diagnostic and demonstrated its prevalence, its use today is increasingly limited by the use of CT and especially high-resolution computed tomography (HRCT) techniques. On HRCT sections, the inner diameter of the bronchus is larger than the adjacent pulmonary artery (if this appearance is perpendicular to the plane of the section, the pathognomonic "stony ring" appearance is formed), the bronchial lumen does not narrow towards the periphery, the bronchus is seen within 1 cm of the pleura and air-fluid levels are evaluated in favor of bronchiectasis.

Bronchoscopy: It should be performed to identify the bleeding site, to elucidate the cause of bronchial obstruction, and to obtain bronchial lavage if infection is suspected and the patient is unable to give a sputum sample.

Pulmonary Function Testing (PFT): In bronchiectasis, impairment of lung function depends on the character and degree of morphological abnormalities in the enlarged bronchial areas, the extent of these areas, and the degree of chronic inflammatory changes and emphysema present in other lung parenchyma and bronchi. A group of patients may have normal spirometric tests. Most patients have diffuse obstructive disorders (decreased FEF25-75 and FEV1/FVC). However, there may be no correlation between dysfunction and the number and type of bronchi affected. If atelectasis and fibrosis develop, a combined pattern may be observed.

Arterial Blood Gas; hypoxemia can often be seen. Sometimes hypercapnia may also be found in these people. Gas exchange may also be impaired due to impaired ventilation and perfusion.

Differential Diagnosis: Chlorine in sweat test, IgG level in young patients with a history of recurrent pneumonia, when ABPA is suspected (asthmatic disease, peripheral eosinophilia, lung infiltrations, proximal bronchiectasis) Positive reaction in skin test against A. fumigatus, elevated IgE, presence of precipitating antibodies, peripheral eosinophilia may be helpful.

Prognosis and Complications: While there was a poor prognosis in the absence of antibiotic use, today, effective antibiotics and chest physiotherapy have improved the prognosis by reducing lung function loss. Chronic respiratory failure and cor pulmonale may occur due to chronic obstructive airway pathologies accompanying bronchiectasis. The most common complications are recurrent pneumonia, empyema, pneumothorax, hemoptysis requiring surgery, and lung abscess. Very rarely, metastatic brain abscess or amyloidosis may occur. Chronic pulmonary infection with pathogenic microorganisms (especially Pseudomonas) has been associated with lower quality of life and mortality (Flume et al., 2018). Systemic

inflammation in bronchiectasis may have important systemic consequences, such as an increased incidence of metabolic or cardiovascular disease. Furthermore, some nutritional and metabolic changes and muscle dysfunctions have also been associated with excessive systemic inflammation in bronchiectasis (Despotes et al., 2020). There are reports of coronary artery calcification, endothelial dysfunction, aortic stiffness, and atherosclerosis in bronchiectasis patients with cardiovascular risk factors (Gao et al., 2018; Saleh et al., 2017).

Treatment: The aim is to control symptoms and prevent progression.

Management to be adopted in patients with bronchiectasis;

- Investigation and treatment of underlying diseases
- Ensuring bronchial hygiene
- Respiratory physiotherapy
- Reduction of excessive inflammatory response
- Treatment of attacks
- Prophylactic antibiotic therapy
- Control of hemoptysis
- Surgical treatment
- General recommendations, training

Bronchiectasis exacerbations are the main determinant of healthcare costs and therefore a key target. 50% of patients have at least 2 exacerbations per year and 1/3 require hospitalization. In the published literature on the duration of treatment of acute exacerbation of bronchiectasis, 14 days of antibiotics are recommended since there is no direct evidence supporting treatment durations of less than 2 weeks and 2-3 weeks. Short-term treatment may be given in patients with mild exacerbation, antibiotic-sensitive pathogen (s. pneum.), and rapid clinical improvement. At the onset of exacerbations, it is recommended to send a sputum sample before starting empirical antibiotic treatment and to give antibiogram-appropriate treatment if the response to initial treatment is inadequate. (Polverino et al., 2017).

Eradication Therapy;

Eradication antibiotic therapy is recommended for bronchiectasis patients with P. aeruginosa growth in culture for the first time, but eradication antibiotic therapy is not recommended for patients with isolation of new pathogens other than P. aeruginosa due to antibiotic resistance problems.

Recommended eradication therapy;

Ciprofloxacin 2x750mg for 2 weeks, followed by IV antipseudomonal therapy for 2 weeks, followed by inhaled tobramycin/ gentamicin/colistin

or

IV antipseudomonal therapy for 2 weeks, followed by inhaled tobramycin/ gentamicin/colistin

or

Ciprofloxacin or IV antipseudomonal therapy (e.g. beta lactam+aminoglycoside) + inhaled tobramycin/ gentamicin/colistin for 2 weeks, followed by inhaled tobramycin/ gentamicin/colistin for 3 months.

Inhaled corticosteroids;

Routine inhaled corticosteroid treatment is not recommended for adults with bronchiectasis. It should only be used in patients with an indication of concomitant asthma or COPD.

Macrolides as anti-inflammatories;

- They reduce the release of proinflammatory cytokines.
- They reduce neutrophil migration.
- They prevent P. aeruginosa from forming a biofilm layer.

Long-term antibiotic treatment;

Long-term (>3 months) antibiotic treatment is recommended for patients with bronchiectasis who have three or more exacerbations per year. Long-term treatment with inhaled antibiotics is recommended for adults with bronchiectasis and chronic P. aeruginosa infection.

Mucoactive treatment;

It is recommended in patients who cannot expectorate sputum and who have a decrease in quality of life due to this reason. Airway clearance medical treatment methods;

- Moisturizing
- Nebulized saline
- Nebulized hypertonic saline
- Nebulized terbutaline
- Inhaled mannitol
- Cysteines

Recombinant human DNase (Dornase α) is not recommended for use in patients with non-cystic fibrosis bronchiectasis.

Long-acting bronchodilators;

Routine bronchodilator treatment is not recommended for adult patients with bronchiectasis.

-Before physiotherapy and inhaled mucoactive drugs,

-Bronchodilator therapy may be administered before inhaled antibiotics.

Surgical treatment;

It is recommended in patients with localized disease and a high frequency of exacerbations, although all other aspects of bronchiectasis treatment have been optimized. Surgical treatment of bronchiectasis aims to break the vicious circle in pathophysiology by removing dysfunctional lung segments. The most common indication for surgery is recurrent infections with chronic symptoms such as productive cough, purulent sputum, and hemoptysis.

Segmentectomy, lobectomy, and pneumonectomy are preferable surgeries. Although bilateral bronchiectasis is not an absolute contraindication for surgery, conservative treatment or alternative methods such as bronchial artery embolization in case of massive hemoptysis are generally preferred in these patients. (Polverino et al., 2017). Surgical complications include empyema, bronchopleural fistula, and hemorrhage. In the late period, bronchiectasis may occur again in another part of the lung. In recent years, heart-lung transplantation has been recommended in cases of cystic fibrosis.

Respiratory physiotherapy;

Patients with a chronic cough or who are unable to expectorate sputum should be taught an airway clearance technique to be performed once or twice daily by a trained respiratory physiotherapist. A pulmonary rehabilitation program should be implemented in bronchiectasis patients with low exercise capacity. These programs should be prepared according to the patient's symptom score, physical characteristics, and comorbidities. (Polverino et al., 2017).

Lung transplantation(*Özyürek and Ulaşlı - Chapter 12 Surgery Associated with Chest Diseases .pdf*, n.y.);

Cystic fibrosis accounts for approximately 1 in 10 of the many indications for lung transplantation worldwide.

Parameters used to refer CF patients to a lung transplant center (Chalermskulrat et al., 2006; Kotloff & Zuckerman, 1996; Snell et al., 1993):

- FEV1 decline to 30% or rapid decline in FEV1 despite multidisciplinary treatment, patients infected with NTM or B. cepacia and/or diabetic patients,

- A clinical picture characterized by an increase in the frequency of attacks and accompanied by at least one of the following

  o Development of acute respiratory failure requiring non-invasive mechanical ventilation (NIMV),

  o Increased antibiotic resistance and inadequate recovery after an exacerbation,

  o Deterioration in nutritional status despite supportive treatment,

  o Development of pneumothorax,

  o The presence of life-threatening hemoptysis despite bronchial artery embolization.

The criteria for inclusion on the waiting list for lung transplantation in patients with CF are:

- Chronic respiratory failure (only hypoxaemia with $PaO_2 < 50$ mmHg or hypercapnia with $PaCO_2 > 50$ mmHg),

- Long-term NIMV requirement,

- The development of PHT,

- History of frequent hospitalization,

- Rapid deterioration in respiratory parameters,

- NYHA functional capacity of 4 (Kotloff & Zuckerman, 1996).

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Procalcitonin Sepsis and its Importance in Clinical Situations

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INTRODUCTION

Today, early diagnosis of infectious diseases continues to be an important problem for clinicians. Generally, the use of antibiotics is not recommended in every suspected infection, because problems with bacterial resistance may arise as a result of unnecessary antibiotic use. In addition, it increases the cost of treatment, as it can cause toxic and allergic reactions. Therefore, it is important to have specific markers for bacterial infections in early diagnosis. Recent studies have revealed the importance of using plasma procalcitonin (PCT) levels as a biomarker. PCT is used in the diagnosis of many diseases and one of the most important areas of use in clinics is its use in the diagnosis of sepsis. Sepsis is a potentially life-threatening condition caused by the body's response to an infection. Many laboratory tests related to sepsis have been studied. PCT has been found to increase in infectious diseases, especially sepsis. Detection of PCT levels has an important role in the diagnosis and follow-up of infections. Procalcitonin is a biomarker that is elevated in non-viral usually bacterial infections. Procalcitonin can help clinicians to moderately reduce antibiotic use in critically ill patients. PCT levels are increased in less severe infections as well as in acute exacerbations of chronic obstructive pulmonary disease (COPD) and community-acquired pneumonia (CAP). (Lacona, 2011). The clinical manifestations of bacterial infections are similar to those of non-infectious systemic inflammations and viral infections. Early diagnosis is important in order to prevent unnecessary antibiotic use and reduce treatment costs for patients. In addition, early differential diagnosis of these diseases, which have different treatment and follow-up, is extremely important. (Çolak, 2017).

PCT is a protein that is a peptide precursor. PCT has a molecular weight of 13 kDa and consists of 116 amino acids. (Carrol, 2002). PCT is considered to be the prohormone of calcitonin synthesized in the thyroid gland. Under normal conditions, calcitonin is biosynthesized as PCT, which is present at low levels in the circulation (≤0.1 ng/mL) in the initial period. Human PCT is encoded by the Calc-I gene located on chromosome 11p15.4. PCT synthesis begins with the translation of preprocalcitonin, a 141 amino acid precursor protein, after transcription of the Calc-I gene. PCT has an N-terminal region (N-ProCT), calcitonin, and PCT has a C-terminal region called katacalcin (Bedin F et al. 2023) (Hamade and Huang, 2020). In healthy subjects, plasma concentrations of PCT are in the picogram levels. It is below the levels that current PCT measurement methods can detect (<0.1 ng/ml). All PCT values above 0.5 ng/ml are considered pathological. If the plasma level of PCT is between 0.5-2 ng/ml, it is considered as slightly elevated. Values exceeding 10 ng/ml are considered high, and values up to 1000 are considered very high. Such high PCT values are only seen in severe acute bacterial infections, sometimes in the hyperinflammatory phase of multiple organ failure syndrome and sepsis. PCT values are usually <2 ng/ml in bacterial or non-parasitic diseases. PCT plasma

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concentrations range from 1 ng/ml to 1000 ng/ml in severe bacterial infections and sepsis. (Maisner, 2000) (Table 1).

Table 1. Expected PCT values in different clinical situations (Maisner, 2000).

Clinical Status	**PCT Level (ng/ml)**
Normal people	<0.5
Chronic inflammatory processes and autoimmune diseases	<0.5
Viral infections	<0.5
Mild to moderate bacterial local infections	<0.5
Systemic inflammatory response syndrome	0.5-2
Multiple trauma	0.5-2
Burns	0.5-2
Serious bacterial infections	>2 (often 10-100)
Sepsis	>2 (often 10-100)
Multiple organ failure syndrome	>2 (often 10-100)

Sepsis is the loss of organ function that occurs as a result of the irregular immunological state of the body against infection (Michael 2017). Sepsis is a complex inflammatory disease that can occur with all kinds of microorganisms and/or their products (Lakshmikanth, 2016). The increase in the elderly population with the increase in systemic diseases has increased the incidence of sepsis. For this reason, it is increasing gradually with the diagnosis of sepsis and the widespread application of the coding system in some countries. Sepsis is the leading cause of death in intensive care units all over the world (Lakshmikanth, 2016) (Dellinger, 2013).

Sepsis is not a notifiable disease, so it is impossible to give exact figures on the actual incidence of sepsis. However, host and environmental factors are effective in the formation of sepsis. Therefore, its frequency varies between patient populations. There is not enough data on the incidence of community-acquired sepsis in our country. However, the incidence of nosocomial bacteremia/sepsis in ICU is reported to be between 7.6-15.8% (Öncü, 2006).

Although the incidence of sepsis varies from hospital to hospital, the number of hospital-acquired sepsis is increasing day by day. Among the most important reasons for the increase in the incidence of sepsis in the community; the increase in the elderly population, the prolongation of the life expectancy of patients with chronic diseases, the increase in the use of immunosuppressive drugs and the widespread use of invasive techniques for diagnosis or treatment (Doğanay, 2002)

The presence of two or more of the following substances is called systemic inflammatory response syndrome (SICS). The presence of proven infection with SICS is called sepsis.

- Heart apex beat >90/min,

- Leukocyte count >12000/mm3 or <4000/mm3 or presence of >10% rod cells in peripheral smear,

- Body temperature above 38 °C or below 36 °C,

- Respiratory rate >20/min or PaCO2 <32 mmHg,

Early clinical signs and symptoms of sepsis may be nonspecific. Early signs of the passage of microorganisms into the bloodstream; There may be symptoms such as chills, chills, fever, malaise, fatigue, somnolence, confusion, nausea, vomiting, and hyperventilation. These symptoms vary according to the severity of the disease (Singer, 2016) (Purcarea, 2020)

In recent years, PCT has been the focus of attention and research as a new biomarker used in the diagnosis and prognosis of patients with severe infections. The test has received particular discussion for use in the differential diagnosis of high-risk and high-cost bacterial infections in patients, particularly sepsis and respiratory diseases (Gyawali, 2019) (Harrison 2015)

Many biomarkers have been routinely used for the diagnosis and prognosis of sepsis, but there is no gold standard test. It has been shown in many studies that PCT can be one of the important and prognostic markers for sepsis (Tan M, et al. 2019). A systematic review and meta-analysis of 30 observational ICUs and non-ICUs in 2013. A study was conducted evaluating PCT as a diagnostic marker of sepsis in critically ill patients. The sensitivity and specificity values obtained in this study were 0.77 (95% CI: 0.72–0.81) and 0.79 (95% CI: 0.74–0.81), respectively. The study concluded that PCT is a potentially useful marker for the identification of sepsis when interpreted with caution in the context of clinical presentation. (Wacker C et al. 2013).

CONCLUSION

PCT is used in many clinical situations and has an important value especially in the diagnosis, treatment and follow-up of sepsis.

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Tricyclic Antidepressant Poisoning

Erdinç ŞENGÜLDÜR

Introduction:

Tricyclic andidepressants (TCA) were first used in the 1950s. They were among the first antidepressant drugs to be used. They have been used in the treatment of depression and other psychiatric disorders for many years. Side effects due to TCA overdose were first reported in 1959 (Lancaster & Foster, 1959). Although safer antidepressant drugs have been produced over the years in terms of side effect profile, TCAs are still widely prescribed worldwide. TCAs are still used in the treatment of obsessive-compulsive disorder, attention deficit hyperactivity disorder, neural pain, chronic pain and migraine (Mandour, 2012). TCA poisoning deaths account for 18% of poisoning deaths in the United Kingdom (UK) (Kerr, McGuffie & Wilkie, 2001). TCAs are among the most commonly used drugs for suicide. Compared to other antidepressants, the ratio of overdose-related deaths to the number of prescriptions written is quite high (Henry, Alexander & Sener, 1995). In the UK, 272 deaths due to TCA overdose were reported in 2005 (Body & et al., 2011).

Inhibition of presynaptic norepinephrine and serotonin reuptake is the main mechanism of effect of TCAs, but it is not the only effect of TCAs in the body. TCAs also

- Block fast sodium channels in the heart.
- Antagonize central and peripheral muscarinic acetylcholine receptors.
- Antagonize alpha1 adrenergic receptors
- Antagonize histaminic H1 receptors.
- Antagonize GABA A receptors.

In excessive intake, side effects and fatal conditions occur due to all these mechanisms of action (Kerr, McGuffie & Wilkie, 2001).

Pharmacokinetics:

TCAs consist of a 3-ring aromatic core and an aliphatic aminopropyl side chain attached to it. The structure of the side chain makes the difference between various drugs. Tertiary amines such as amyltriptyline and imipramine undergo demethylation in the liver and form secondary amines with metabolic activity. Amyltriptyline is converted to nortriptyline. Imipramine is converted to desipramine. Amyltriptyline and imipramine levels measured in the laboratory reflect both tertiary amines and their active metabolites (Glauser, 2000).

TCAs are rapidly absorbed from the gastrointestinal tract. They reach peak serum concentrations between 2 and 8 hours. Elimination times depend on liver metabolism and vary from person to person. They are partially secreted into bile, reabsorbed from the intestine and excreted from the kidney. TCAs are highly bound to plasma proteins and have a large volume of distribution and therefore a long elimination half-life. The elimination half-life of TCAs is

usually over 24 hours. The elimination half-life of amyltriptyline can be as long as 31 to 46 hours (Kerr, McGuffie & Wilkie, 2001)

The pharmacokinetics of the drug is different in overdoses compared to therapeutic doses. Due to anticholinergic effects, bowel movements slow down and drug absorption decreases. Since the enzymes that metabolize TCAs become saturated, the elimination of the drugs in the body slows down in overdose. Acidemia decreases the binding of TCAs to plasma proteins, the amount of free drug in plasma increases. The sum of all these effects results in delayed absorption, increased active drug ratio and delayed excretion (Van de Wint & et al., 2022).

Pharmacodynamics:

The clinical effects of TCA overdose can be divided into 3 groups: anticholinergic effects, cardiovascular effects and central nervous system effects.

Anticholinergic Effects: Anticholinergic findings are frequently seen in cases of TCA intoxication and are helpful in making the diagnosis. Although serious clinical results do not usually occur due to anticholinergic effects, it has been shown that serious conditions such as toxic megacolon and intestinal perforation may develop (McMahon, 1989).

Cardiovascular Effects: TCAs block fast sodium channels in His-Purkinje fibers and myocardium, therefore cardiac conduction abnormalities are observed in TCA intoxication. Conduction velocity decreases, repolarization time prolongs and absolute refractory time increases (Glassman, 1984). This effect of TCAs on the heart is similar to class 1A antiarrhythmic drugs. The mechanisms causing hypotension in poisoning cases include decreased calcium influx into ventricular myocytes, blockade of fast sodium channels and peripheral vasodilation resulting from blockade of alpha 1 adrenergic receptors.

Effects on the Central Nervous System: Various levels of central nervous system depression may occur. Confusion, lethargy, stupor and even cognitive impairment progressing to coma may develop. Seizures may occur in TCA poisoning due to antagonist effects on GABA-A receptor (Olson & et al., 1994). Most seizures are of short duration and self-limiting, but some seizures may be persistent and may be accompanied by cardiovascular pathologies. Maprotiline has been associated with a higher frequency of seizures and arrhythmias than other TCAs (Ellison & Pentel 1989).

Clinical Assessment:

Anamnesis: The patient's comorbid diseases, medications used, drugs thought to cause intoxication should be asked. It should be learned when and in what quantity the drugs causing intoxication were taken.

Physical Examination: The typical symptom of TCA intoxication is sedation. However, lethargy, stupor and even coma may be observed depending on the level of intoxication. Delirium and hallucinations may also be observed. Hypotension is an expected finding. Anticholinergic symptoms are common, hyperthermia, flushing of the skin, dilated pupils may be seen. Due to the variable pharmacokinetics of TCAs, patients with subtle findings at presentation may deteriorate rapidly afterwards. At 10 - 20 mg/kg TCA intakes, serious central nervous system and cardiovascular system symptoms may occur (Liebelt, 2011).

Sinus tachycardia and hypotension are common findings in TCA intoxication. Refractory hypotension is an important cause of death in TCA intoxication. Cardiac conduction abnormalities and alpha1 adrenergic receptor antagonism are the cause of developing hypotension (Shannon, Merola & Lovejoy, 1988). Ventricular tachycardia (VT) and ventricular fibrillation (VF) may occur in a small proportion of poisoning cases. It is more common in

severe poisoning, especially in cases with QRS prolongation on electrocardiogram (ECG) (Goldberg, Capone & Hunt, 1985).

Diagnostic Tests:

Various laboratory tests and investigations can be performed to make a diagnosis, estimate the severity of poisoning and rule out additional toxicities. Measurement of plasma TCA ratio is not a widely available test. The TCA level, which is available in a few centers, is not useful because it does not detect active metabolites.

ECG: Cardiac conduction abnormalities are common in patients with TCA poisoning. Therefore, in patients with known or suspected TCA poisoning, it is essential to perform an ECG immediately after presentation. In a study, it was shown that the rate of seizures, coma and cardiac arrest was high in patients with plasma TCA levels >1000 mg/L (Petit & et al., 1977). However, QRS prolongation on ECG is a better marker for seizures and ventricular arrhythmias (Boehnert & Lovejoy, 1985). Arrhythmia may develop rapidly in TCA poisoning. ECGs should be taken frequently during patient follow-up. Hourly ECG monitoring is recommended, but more frequent ECGs are necessary if the patient develops signs of cardiotoxicity or if conduction abnormalities are seen on the initial ECG or cardiac monitor (Body & et al., 2011).

Cardiotoxicity should be considered in the following cases: QRS prolongation >100 msec, abnormal morphology of the QRS, abnormal size and ratio of R and S waves in the aVR lead. These ECG changes are used for diagnosis and risk stratification, but none are completely reliable in all patients. Severe toxicity may also develop in cases without ECG changes, or the patient may have pre-existing conduction defects that make diagnosis difficult (Harrigan & Brady, 1999).

QRS duration >100 milliseconds on ECG is a marker for potential cardiotoxicity and determines the indication for IV sodium bicarbonate treatment.

Prolongation of PR and QT intervals and bundle branch block are also ECG changes that may be observed in TCA intoxication. The right bundle branch is more sensitive because of the longer refractory period. These conduction system abnormalities may cause the hypotension seen in TCA intoxication. Although QT prolongation is common in TCA overdose, polymorphic ventricular tachycardia and Torsade de Pointes associated with QT prolongation are not common (Niemann & et al., 1986).

Case Management and Treatment:

Treatment of tricyclic antidepressant (TCA) poisoning begins with evaluation of the patient's airway, respiration and circulation. Patients poisoned with TCA are often morbid and require intubation for airway protection and ventilation. Supplemental oxygen should be administered as needed. Gastric decontamination is also useful at TCA poisoning.

Sodium bicarbonate is given to treat cardiac toxicity manifested by prolonged QRS duration or ventricular arrhythmia. In case of hypotension, saline is given as first choice. A 500 cc bolus is given, repeated if necessary. Benzodiazepines are used to control agitation. If necessary, lorazepam (1 mg IV) or diazepam (5 mg IV) repeated at 5 to 10 minute intervals is recommended. Benzodiazepines should be used with caution as agitation may rapidly give way to deep sedation. Although marked anticholinergic findings are seen in TCA poisoning, the use of physostigmine is contraindicated because it is associated with cardiac arrest (Body & et al., 2011).

Gastrointestinal Decontamination: Gastric lavage is most effective when performed within the first few hours. However, since TCAs also delay gastric emptying, gastric lavage is

also useful in the following hours. Treatments such as Ipeka syrup that cause the patient to vomit and empty the stomach should not be used because they increase the risk of aspiration. Activated charcoal binds TCAs and can be given 30-50 grams through nasogastric cannula in TCA poisoning (Glauser, 2000).

Sodium Bicarbonate Treatment: In patients with TCA poisoning, sodium bicarbonate treatment should be started if QRS >100 milliseconds or ventricular arrhythmia is observed on ECG. 1-2 meq/kg IV is given as a push. If there is no narrowing in the QRS interval, it is repeated after 5 minutes. After narrowing of the QRS interval is observed, infusion treatment is started. 60 meq sodium bicarbonate is given in 1000 cc of 5% dextrose at a dose of 2-3 cc/kg/hour. The target serum pH is between 7.45-7.55. Potassium should also be given to the patient if necessary. Absence of narrowing in the QRS interval after the push doses does not exclude the diagnosis of TCA intoxication. Infusion dose should be started even if the QRS interval does not narrow after the push doses. Prolonged bicarbonate infusions may cause volume overload, hypokalemia, hypernatremia and metabolic alkalosis and clinical and laboratory parameters should be closely monitored to avoid these complications. Arterial pH is measured hourly until it is within the therapeutic range and stable. Thereafter, measurements can be made every four to six hours (Glauser, 2000). The majority of patients with QRS prolongation and hypotension due to TCA poisoning achieve clinical improvement with sodium bicarbonate treatment.

The therapeutic activity of sodium bicarbonate occurs because it increases serum pH and increases the amount of free sodium. As serum pH increases, TCAs bind less to sodium channels. Increasing serum sodium concentration alleviates the blockade of sodium channels.

Hyperventilation increases serum pH by decreasing pCO2. In a retrospective case series, reduction of pCO2 (to a mean of 36 mmHg) combined with sodium bicarbonate administration led to a more rapid reduction in QRS duration and a greater increase in serum pH (Pai & et al., 2022). However, intubating and hyperventilating patients in TCA poisoning is not a recommended treatment method due to lack of sufficient clinical data.

Seizure Treatment: Seizures due to TCA poisoning are usually short-lasting. The cause of seizure development in TCA intoxication is inhibition of GABA A receptors, therefore it is logical to use benzodiazepine group drugs acting through GABA-A receptors. The first preferred drug group is benzodiazepines. Dizaepam 0.1 mg/kg and lorazepam 0.04 mg/kg are used. If seizure control cannot be achieved, barbiturates may also be used, but they should be considered as second-line drugs because of their negative effects on blood pressure. Phenobarbital can be used at a dose of 15mg/kg. Propofol is effective on both GABA and NMDA receptors. It can be used as a last resort. It is administered at a dose of 1mg/kg (Chen, Albertson & Olson KR, 2016).

Hypotension Treatment: In TCA poisoning, hypotension is expected to improve with IV fluid therapy and sodium bicarbonate treatment. In cases where hypotension is resistant, hypertonic sodium chloride (3% NaCl) or vasopressors may be used. Alpha adrenergic agonists are preferred because they counteract the alpha adrenergic antagonist effects of TCAs. Vasopressors such as noradrenaline and phenylephrine are titrated to the appropriate dose and given by IV infusion. In patients whose hypotension does not improve despite improvement of arterial pH and who do not respond to appropriate vasopressor treatment, 3% NaCl treatment may be administered. 3% saline is given as a 100 mL IV bolus; if symptoms persist, two more doses can be given at ten-minute intervals. Additional hypertonic saline should not be given and serum sodium concentration should be monitored (Glauser, 2000).

Treatment of Refractory Arrhythmias: There are studies showing the efficacy of magnesium and lidocaine in cardiac arrhythmias that persist despite bicarbonate therapy, but

neither lidocaine nor magnesium are the first choice drugs in the treatment of arrhythmias developing in TCA poisoning. there is no standard dosage recommendation for magnesium. As an appropriate approach, 1-2 g can be given within 15 minutes if the patient is in cardiac arrest. Lidocaine can also be used in cases where there is no response to sodium bicarbonate treatment. Lidocaine is used in standard anti-arrhythmic doses as a bolus dose (1 to 1.5 mg/kg IV) followed by infusion (1 to 4 mg/min) (Body & et al., 2011).

Lipid Emulsion Therapy: TCAs are highly lipophilic drugs. Increased amount of lipids in plasma has been shown to bind TCAs and decrease their bioavailability. When lipid emulsion is administered, increased plasma lipid level also increases free fatty acid availability in the myocardium. As a result of these effects, cardiotoxicity may be reversible (Blaber & et al., 2012).

Lipid emulsion is a promising treatment for TCA poisoning. However, there are not enough studies showing that lipid emulsion treatment is as effective as standard treatment in TCA poisoning. Lipid emulsion therapy can be used in TCA poisoning in the presence of life-threatening cardiovascular findings that do not respond to other treatments (Body & et al., 2011).

In treatment, 20% lipid emulsion solutions are used. 1-1.5 mL/kg iv bolus dose is used. In patients with cardiac arrest, a total of 3 doses can be administered every 5 minutes. Infusion at a dose of 0.025 mL/kg can be started from the first bolus dose until hemodynamic recovery is achieved, this infusion can be continued for up to 60 minutes. The maximum dose for lipid emulsion is 10 mL/kg (Spray, 2016)

Conclusion:

TCA poisoning is still common and can cause fatal outcomes. TCA intake should be questioned in patients with confusion, cardiac rhythm disorders and anticholinergic findings. It should be kept in mind that even if patients appear well at the time of presentation, the clinical condition may rapidly deteriorate. Since the metabolism of the drug may vary from person to person, it should be kept in mind that intoxications that do not involve very high doses may also have a poor prognosis. TCA poisonings are serious cases. They should be watched closely and under cardiac monitoring.

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Evaluation of Unknown Reasons of Completed Suicides in terms of Geographical Regions in Turkey: A retrospective study – 45 years

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Introduction

It is observed that the crude suicide rate has increased approximately 2.5 times in the years between 1975 and 2019 in Turkey, with suicides of an unknown reason accounting for a significant part among completed suicides. However, very limited information is available about completed suicide of an unknown reason.

This study was conducted to compare completed suicides of an unknown reason by geographical regions in Turkey.

In this study, suicide statistics of the Turkish Statistical Institute (TURKSTAT) for the years between 1975 and 2019 were analyzed retrospectively. The distribution of completed suicides of an unknown reason was examined by geographical regions for the specified period of 45 years. Data were evaluated by numbers, percentages, and mean and standard deviation. RMANOVA, Duncan's multiple comparison test, and Bonferroni's multiple comparison test were used.

The review of the total number of suicide cases per 100,000 population in seven geographical regions of Turkey in a period of 45 years reveals that suicides were most common in the Aegean region followed by the Eastern Anatolia, Mediterranean, Central Anatolia, Black Sea, Marmara, and Southeastern Anatolia regions, respectively. However, the examination of suicides of an unknown reason reveals that the rates were the highest in the Eastern Anatolia region, which was followed by the Aegean, Black Sea, Mediterranean, Southeastern Anatolia, and Marmara regions, respectively in the decreasing order of frequency.

This study has shown that suicides of an unknown reason constituted the most significant category among completed suicides by the reason in Turkey in the years between 1975 and 2019. It has been found out that suicides of an unknown reason in Turkey were most common in the Eastern Anatolia region and least common in the Marmara region.

About 800,000 people die each year due to suicide. This figure means that one person dies every forty seconds due to suicide.[1] It is the responsibility of all healthcare professionals to recognize suicide with every aspect and to carry out preventive activities in order to forestall suicide, which is a social problem.[2] It is imperative to focus on reasons for suicide prevention.

Many factors are involved in leading a person to commit suicide. These factors are grouped into categories of individual (a previous suicide attempt, mental illness such as depression, social isolation, criminal problems, financial problems, impulsive or aggressive tendencies, job problems

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or job loss, legal problems, serious illness, and substance use disorder), relationship (adverse childhood experiences such as child abuse and neglect, bullying, family history of suicide, relationship problems such as a break-up, violence, loss, and sexual violence), community (barriers to health care, cultural and religious beliefs such as a belief that suicide is noble resolution of a personal problem, and a suicide cluster in the community), and social (stigma associated with mental illness or help-seeking, easy access to lethal means such as firearms or medications, and unsafe media portrayals of suicide).[3] When the reason(s) of suicide is/are known, health care workers will take healthcare measures for prevention. However, when reasons are unknown, healthcare services to be provided will not achieve desired goals adequately.

Turkey is among the countries with low suicide rates. Rates of suicide-related deaths are very low in Turkey compared to European countries.[4] However, it is thought-provoking that the reason of the majority of suicides in Turkey in recent years is unknown.

Turkey consists of seven geographical regions, namely the Marmara, Aegean, Mediterranean, Central Anatolia, Black Sea, Eastern Anatolia, and Southeastern Anatolia regions. In this study, the geographical regions of Turkey were examined individually. It is suggested that the demographic structure, population, and social, economic, and cultural characteristics of the abovementioned regions can significantly act on the reasons of completed suicides.

Results obtained from retrospective studies on completed suicide cases will affect the approaches towards people, who have attempted suicide and survived or who have suicidal ideation. In addition to social support, healthcare support should be provided to people, who are at risk of committing suicide. Accordingly, risk groups should be identified and preventive programs should be developed and implemented.

There is no 100% accuracy or scientific precision in scientific research on suicide and suicide statistics by countries. This may be reasond by the use of different registration systems by the police, security forces, and hospitals. Furthermore, it can be suggested that the phenomenon of suicide can be affected by the interplay of many factors ranging from political, religious, social, and personal variables to the concealment of cases either deliberately or inadvertently.[4]

Some of the difficulties frequently encountered in obtaining information about suicide include the involvement of political, religious, and cultural elements, avoidance to speak about suicide, improper registration systems, biased statistics due to some reasons, and the lack of an identifiable reason of death.[2,5,6] Therefore, it is not easy to find out the full reason for completed suicide.[7]

If the geographical regions of Turkey with high numbers of completed suicides of an unknown reason are identified, it will be easier to take protective measures accordingly. This study was planned from this point of view and carried out in order to compare completed suicides of an unknown reason by geographical regions of Turkey.

Methods:

In this retrospective study, suicide statistics of the Turkish Statistical Institute (TURKSTAT) covering the years between 1975 and 2019 were reviewed. TURKSTAT is the official organ of the state to compile and publish suicide statistics in Turkey. TURKSTAT has started to publish information on completed suicides since 1962. As of 1974, "Suicide Statistics" booklets have been published, which can be purchased by researchers for a fee. Completed suicides recorded for each settlement unit until the year 2012 were retrieved from the records of the General Directorate of Security and the General Command of Gendarmerie. Completed suicides occurring since 2012 were retrieved including the information obtained from death certificates and records of the Ministry of Justice, the General Directorate of Prisons and Detention Houses. Since 2012, TURKSTAT has published suicide statistics on its official website (www.tuik.gov.tr) but not in print.[8]

In this study, suicide statistics were reviewed for completed suicides of an unknown reason by geographical regions covering a period of 45 years (1975-2019). TURKSTAT's internet database and printed sources by TURKSTAT were utilized to calculate numbers and percentages using the obtained information. There was no need to obtain permission or ethical approval for the use of the data published on the Internet and made available to everyone.

Statistical analyses of the study were performed using the Statistical Package for Social Sciences for Windows (IBM SPSS version 25.0, Armonk, NY, USA) software. The normality assumption of continuous variables was tested with the Kolmogorov-Smirnov and Shapiro-Wilk tests. In addition, histogram graphs of the data were examined for testing the normality. Descriptive statistics of the variables were presented in mean ± standard deviation. Bereason observations were obtained from the same regions on 24 different dates, the Repeated Measures Analysis of Variance (RMANOVA) method was used for comparisons. Differences between regions were compared using the Duncan multiple comparison test. Differences between years were compared using the Bonferroni multiple comparison test. In all statistical analyses, $p<0.05$ was interpreted as statistically significant.

Results

It was found out that 88,044 suicide cases were completed over a period of 45 years in the years between 1975 and 2019 in Turkey. While the number of suicides across the country was 788 in 1975, it reached 3,406 in 2019. Reasons of suicide were unknown in 26,247 (29.81%) completed suicide cases (Tables 1 and 2).

When suicides of an unknown reason were examined among all suicides by geographical regions, it was observed that the rate of suicides of an unknown reason was significantly higher in the Southeastern Anatolia region in the years between 1978 and 1984 compared to other regions. After 2011, the Eastern Anatolia region started to come to the forefront (Figure 1). The examination of rates of suicides of unknown reason among completed suicides by the geographical region revealed that rates were higher in the Eastern Anatolia (38.4%) and Southeastern Anatolia (37.4%) regions compared to other regions (Table 2).

Rates of completed suicides in Turkey were highest in the Marmara region (26.7%) followed by the Aegean (19%), Central Anatolia (16.9%), Mediterranean (11.7%), Black Sea (9.8%), Southeastern Anatolia, (8.2%) and Eastern Anatolia (7.9%) regions, respectively. Of rates of suicides of an unknown reason among completed suicides by geographical regions, the two highest rates were found in the Eastern Anatolia (0.383) and Southeastern Anatolia (0.376) regions. The Marmara region was a region with one of the lowest levels (0.277). It is thought that the Marmara region ranked first bereason of its more crowded population compared to other regions (Table 2).

The distribution of suicide cases in Turkey by regions per 100,000 population in the years 1975-2019 is presented in Table 3. Based on the figures in Table 3, the difference in the distribution of suicide cases of an unknown reason was statistically significant between geographical regions **(p=0.000).** The number of suicide cases of an unknown reason in Turkey was found to be highest in the Eastern Anatolia region (1.99), followed by the Aegean (1.61), Black Sea (1.39), Mediterranean (1.31), Southeastern Anatolia (1.25), and Marmara (1.09) regions in the decreasing order of frequency. The distribution of overall suicide attempts, too, was statistically significant between geographical regions **(p=0.000).** Overall suicide attempts were most common in the Aegean region (4.33) followed by the Eastern Anatolia (4.24), Mediterranean (4.14), Central Anatolia (3.66), Black Sea (3.46), Marmara (3.31), and Southeastern Anatolia (2.93) regions, respectively (Table 3).

The examination of suicide cases in Turkey by the year in the period specified for the study showed that the distribution of completed suicides of an unknown reason and the distribution of

all completed suicides were statistically significantly different between years **(p=0.000)**. Based on data obtained from TURKSTAT, the numbers of suicides of an unknown reason were zero in 1997, 1998, 1999, 2000, 2001, 2002, and 2003. Of completed suicides of an unknown reason, the lowest number of cases per 100,000 population was detected in 1990 with an average of 0.06 and the highest number of cases was recorded in 2016 with an average of 2.65. Of overall suicides per 100,000 population, the least number of cases was detected in 1980 with an average of 1.68 and the highest number of cases was detected in 2006 with an average of 4.55 (Table 4).

When suicide cases were compared based on whether a reason was identified or not, it was observed that a reason was identified in 87.3% of suicide cases in 1975. This figure varied from 60% to 80% in the period between 1976 and 1986, it was 82.7% in 1987, and it remained above 90% in the years from 1988 to 1997. It was observed that rates of suicide of an unknown reason were in the range of 40-60% from 2004 to 2016, reached a peak at 61.3% in 2016, and gradually decreased after 2016 (Table 2).

Discussion

Suicide is a common social problem worldwide and many people end their lives intentionally every year around the world.[4] In this study, similar to the findings in the study by Öztürk and Öztürk (2021), it has been found out that the number of suicides of an unknown reason is increasing every year. In order to reduce suicide rates to the lowest possible levels, it is essential to establish reasons of suicide. [9]

Such high rates of suicide of an unknown reason suggest that suicide cases have not been adequately examined retrospectively, that is, a psychological autopsy has not been performed satisfactorily. The psychological autopsy method involves combining psychiatric information and other information about suicides retrieved from health records and obtained through interviews with community members, who were in interaction with the individual. Psychological autopsy reveals the relationship between suicide and the unfavorable previous life experiences of an individual. In particular, through a retrospective examination, the psychological autopsy method enables the establishment of the relationship between traumatic life events in childhood and adult suicidal behavior.[10]

Another aspect of the findings of this study leads us to the suggestion that professionals in security forces and hospital officials do not document reasons of suicide adequately bereason they prefer not to go into the details of the case. They may prefer to fill out forms as soon as possible just to carry out a task perfunctorily. They might experience difficulties obtaining information about one or more actual reasons of suicide bereason relatives of the person, who attempted or committed suicide, might be going through a traumatic experience by the time of the incident. It is observed that officials in charge of documentation cannot fulfill their duties adequately. Consequently, reasons remain unknown in almost half of all suicide cases. This situation makes it difficult to derive sound conclusions and develop solutions.

The category of the suicide of an unknown reason with the inclusion of more than 50% of suicide cases in some years reflects this situation. The main factor leading to such a situation is that relatives of the suicide victim, who are influenced by the disapproval of society regarding suicide, are reluctant to disclose the real reason/reasons behind the suicide or officials may be documenting the declared reason in the known category.[11]

In Table 2, it is observed that the number of suicides of an unknown reason was consistently zero in each region in the years between 1997 and 2004. Although this may indicate that the goal of identifying reasons of suicide has been achieved, the rate of 47.4% (1,283) for suicides of an unknown reason in 2004 suggests that figure zero is not realistic. Taking the political and economic crises in the country in that period into consideration, the negligence of officials may be the reason of documented figure zero.

All suicide cases are considered judicial in Turkey and such information is included in police and gendarmerie reports. The prosecutor's office is involved in cases of death. When it is deemed necessary, the case is referred to Forensic Medicine. As it is known, suicides are usually recorded by officials of security forces (police and gendarmerie) and by professionals in emergency departments of hospitals. It is obvious that these units, which act independently of each other, do not obtain adequate information about suicide.

Similar to the finding of this study, Alptekin and Duyan (2014) found that suicide rates increased in eastern and northern Turkey.[5] A literature review showed that an increase in suicide cases especially in the Eastern and Southeastern Anatolia regions after the year 2000.[7,12-14] Along with the increase in suicide cases, it has been observed that the reasons for suicides in these geographical regions are not known adequately.

Climate characteristics, natural living conditions, sources of income, industrialization, education, demographic structure, and customs and traditions vary across the geographical regions of Turkey significantly. The welfare level is higher in the Aegean, Marmara, and Mediterranean regions in the west of Turkey, whereas the welfare levels of the Eastern and Southeastern Anatolia regions are lower compared to other geographical regions.[5] Welfare levels may be one of the reasons why reasons of suicide are inadequately known in these regions. Furthermore, the wide spacing of settlements and houses, the psychological effects of the overclouded and rainy weather on individuals, and the widespread use of fire guns in the Black Sea region are important factors leading to increasing suicide rates.

In order to develop effective strategies for the prevention of completed suicides, it is obvious that the level of uncertainty in the reasons of suicide should be reduced. Therefore, it is essential that security and health officials should collect actual information on the reasons of suicide, in compliance with professional rules and away from subjective evaluations and social prejudices. It is thought that in-depth social studies on the reasons of suicide and the implementation of effective psychological autopsy methods in completed suicide cases may reduce the rates of suicides of an unknown reason.

Ethics Committee Approval: Bereason the study is retrospective and the data are published on the internet and available to public, ethical approval was not required.

Informed Consent: This is a retrospective study.

Peer Review: Externally peer-reviewed.

Author Contributions: Concept – Ş.T.; Design – S.T. ; Supervision – Ş.T. A.Ü.; Materials – Ş.T.; Data Collection and/or Processing – Y.K.; Analysis and/or Interpretation – Ş.T.; Literature Review – Ş.T. A.U.; Writing - Ş.T. A.U.; Critical Review - Ş.T. A.U.

Conflict of Interest: The authors have no conflict of interest to declare.

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Table 1. Reasons of suicide

Total (%)		Illness		Family incompatibility		Economic problems and business failure		Emotional relationship and not marrying the person wanted		Educational failure		Other		Unknown	
No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
88044	100	22390	25.43	13423	15.24	10625	12	5775	6.55	1583	1.79	7707	8.75	26247	29.81

Table 2. Distribution of Suicides of An Unknown Reason by Geographical Regions

Years	Aegean			Marmara			Mediterranean			Central Anatolia			Black Sea			Southeastern Anatolia			Eastern Anatolia			Ukn.		Total
	Kn.	Ukn.	Total	Kn.	Ukn.	Total	Kn.	Ukn.	Total	Kn.	Ukn.	Total	Kn.	Ukn.	Total	Kn.	Ukn.	Total	Kn.	Ukn.	Total	No	%	
1975	81	11	92	275	22	297	44	20	64	139	15	154	70	6	76	26	12	38	53	14	67	100	12.7	788
1976	147	43	190	161	45	206	60	25	85	91	43	134	85	28	113	29	10	39	37	25	62	219	26.4	829
1977	156	46	202	88	63	151	51	28	79	103	60	163	91	24	115	34	13	47	38	29	67	263	31.9	824
1978	139	32	171	61	46	107	48	27	75	96	28	124	56	23	79	7	14	21	33	23	56	193	30.5	633
1979	123	56	179	93	59	152	50	31	81	100	35	135	85	26	111	19	17	36	44	28	72	252	32.9	766
1980	96	63	159	138	74	212	39	31	70	78	34	112	65	22	87	16	20	36	42	32	74	276	36.8	750
1981	141	42	183	192	81	273	38	26	64	121	47	168	49	19	68	32	12	44	50	26	76	253	28.9	876
1982	140	93	233	220	98	318	45	34	79	154	54	208	94	32	126	24	32	56	56	29	85	372	33.6	1105
1983	116	86	202	242	101	343	92	51	143	138	53	191	109	28	137	26	24	50	55	28	83	371	32.3	1149
1984	122	63	185	287	84	371	99	39	138	207	44	251	164	16	180	44	17	61	68	19	87	282	22.2	1273
1985	149	45	194	233	91	324	104	56	160	176	41	217	117	14	131	45	14	59	84	18	102	279	23.5	1187
1986	150	37	187	249	49	298	103	47	150	134	36	170	124	10	134	44	9	53	60	16	76	204	19.1	1068
1987	156	37	193	273	38	311	99	36	135	176	39	215	99	14	113	36	8	44	69	18	87	190	17.3	1098
1988	175	21	196	278	31	309	106	13	119	198	24	222	106	6	112	43	2	45	87	9	96	106	9.6	1099
1989	219	10	229	281	30	311	140	9	149	220	13	233	120	9	129	48	4	52	62	7	69	82	7	1172
1990	301	9	310	309	14	323	182	4	186	239	11	250	121	2	123	78	1	79	85	1	86	42	3.1	1357
1991	303	1	304	270	8	278	164	9	173	209	7	216	132	2	134	50	1	51	72	0	72	28	2.3	1228
1992	233	5	238	301	6	307	154	7	161	207	6	213	95	3	98	63	1	64	86	0	86	28	2.4	1167
1993	217	0	217	347	2	349	151	1	152	226	6	232	112	1	113	80	0	80	86	0	86	10	0.8	1229
1994	269	2	271	455	7	462	221	2	223	283	1	284	94	2	96	98	0	98	99	3	102	17	1.1	1536
1995	240	0	240	416	5	421	236	1	237	271	4	275	122	3	125	73	0	73	87	2	89	15	1	1460
1996	366	1	367	466	8	474	259	4	263	329	2	331	139	1	140	104	4	108	132	0	132	20	1.1	1815
1997	326	0	326	558	0	558	280	0	280	363	0	363	174	0	174	132	0	132	157	0	157	0	-	1990

1998	319	0	319	557	0	557	236	0	236	363	0	363	145	0	145	149	0	149	121	0	121	0	-	1890
1999	333	0	333	499	0	499	234	0	234	344	0	344	139	0	139	158	0	158	146	0	146	0	-	1853
2000	366	0	366	465	0	465	210	0	210	310	0	310	125	0	125	201	0	201	125	0	125	0	-	1802
2001	483	0	483	742	0	742	302	0	302	440	0	440	235	0	235	195	0	195	187	0	187	0	-	2584
2002	483	0	483	582	0	582	257	0	257	411	0	411	171	0	171	212	0	212	185	0	185	0	-	2301
2003	647	0	647	614	0	614	266	0	266	446	0	446	295	0	295	236	0	236	201	0	201	0	-	2705
2004	244	201	445	357	373	730	210	97	307	209	160	369	171	149	320	104	145	249	129	158	287	1283	47.4	2707
2005	265	234	499	369	285	654	235	97	332	213	162	375	206	137	343	102	115	217	138	145	283	1175	43.5	2703
2006	198	217	415	330	371	701	261	112	373	232	212	444	191	156	347	92	134	226	146	177	323	1379	48.7	2829
2007	211	193	404	402	326	728	251	100	351	258	208	466	205	140	345	128	135	263	104	132	236	1234	44.2	2793
2008	280	185	465	447	233	680	267	98	365	312	132	444	185	130	315	134	140	274	159	114	273	1032	36.7	2816
2009	203	318	521	511	285	796	257	121	378	269	201	470	163	152	315	121	140	261	114	134	248	1351	46.6	2989
2010	261	284	545	463	321	784	281	122	403	262	176	438	122	137	259	107	160	267	83	154	237	1354	46.2	2933
2011	202	247	449	434	245	679	243	130	373	246	173	419	117	116	233	96	155	251	91	182	273	1248	46.6	2677
2012	324	310	634	467	485	952	171	162	333	248	281	529	141	140	281	119	214	333	63	162	225	1754	53.4	3287
2013	325	308	633	422	457	879	140	166	306	241	282	523	124	161	285	156	211	367	85	174	259	1759	54.1	3252
2014	303	309	612	440	368	808	160	215	375	232	285	517	103	190	293	142	195	337	64	163	227	1725	54.4	3169
2015	301	320	621	510	328	838	156	167	323	307	242	549	129	150	279	176	199	375	83	178	261	1584	48.8	3246
2016	261	388	649	357	541	898	137	214	351	221	286	507	87	175	262	102	194	296	57	173	230	1971	61.7	3193
2017	328	282	610	531	355	886	204	147	351	341	156	497	101	171	272	197	133	330	114	108	222	1352	42.7	3168
2018	367	318	685	575	384	959	199	130	329	400	161	561	155	142	297	181	113	294	115	102	217	1350	40.4	3342
2019	425	282	707	691	200	891	192	125	317	444	152	596	188	133	321	225	109	334	147	93	240	1094	32.1	3406
		5099	16593		6519	23477		2704	10338		3872	14879		2670	8591		2707	7191		2676	6975	26247	1124	88044
Ukn. / Tot.	0.307			0.278			0.262			0.260			0.311			0.376			0.384			0.298		

Table 3. Distribution of suicide attempts by region in 1975-2019 in Turkey (Per 100,000 population)

Regions of Turkey	**Unknown*** **Mean±SD**	**Total*** **Mean±SD**
Aegean	1.61∓0.76ab	4.33∓1.05e
Marmara	1.09∓0.71a	3.31∓0.49ab
Mediterranean	1.31∓0.85a	4.14∓0.98cd

Central Anatolia	1.18∓0.82a	3.66∓0.76bc
Black Sea	1.39∓0.97a	3.46∓1.17ab
Southeastern Anatolia	1.25∓0.86a	2.93∓0.89a
Eastern Anatolia	1.99∓0.68b	4.24∓1.30cd
P	0.000	0.000

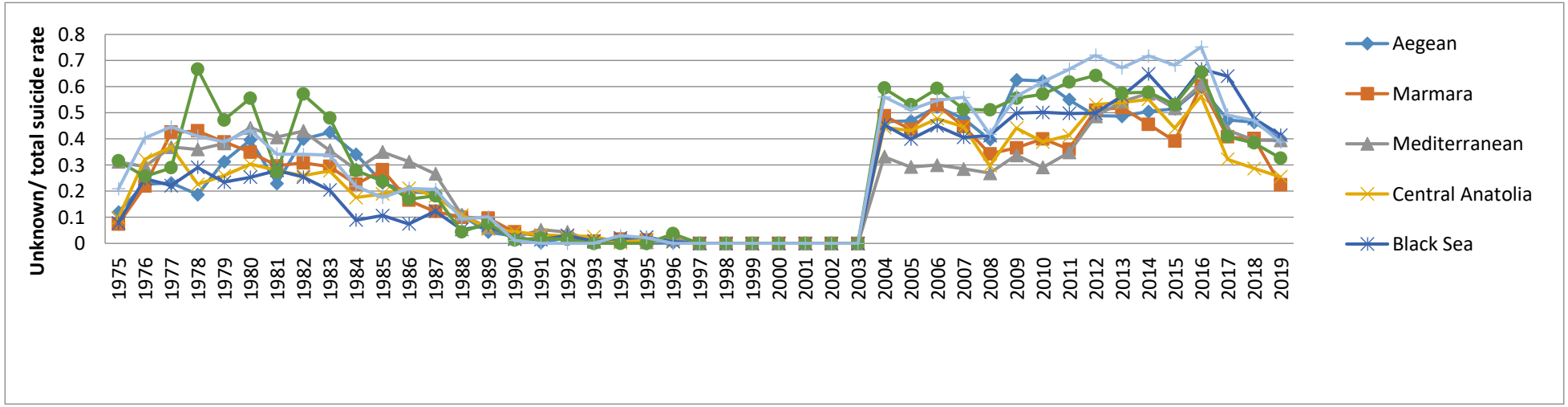
*There is not a statistically significant difference between the means shown with the same letter in the same column (p>0.05)

Table 4. Distribution of suicide attempts in Turkey in the years between 1975 and 2019 (Per 100,000 population)

Years	**Unknown* Mean±SD**	**Total* Mean±SD**
1975	0.29∓0.15b	1.82∓0.79 a
1980	0.65∓0.22b	1.68∓0.50 a
1985	0.54∓0.28b	2.40∓0.60 a
1990	0.06∓0.04b	2.39∓0.88 a
2000	0.0∓0.0a	2.78∓0.57ab
2005	1.93∓0.61cde	4.35∓1.05c
2010	2.09∓0.61cdef	4.18∓0.77c
2015	2.35∓0.67cdef	4.37∓0.58c
2019	1.53∓0.45c	4.28∓0.68c
P	0.000	0.000

*There is not a statistically significant difference between the means shown with the same letter in the same column (p>0.05)

Figure 1. Ratio of suicides with unknown reasons to total suicides in geographical regions



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Shoulder Impingement Syndromes

Melike Elif KALFAOGLU[1]

Introduction

Shoulder impingement syndromes are a common cause of shoulder pain. They can be broadly classified into external (extrinsic) and internal impingements, which involve the entrapment of musculoskeletal soft tissue within the shoulder. External impingements refer to extra-articular impingements of the rotator cuff tendons, while internal impingements are intra-articular impingements of the rotator cuff tendons (Mulyadi&et al.,2009).

The primary symptom of shoulder impingement syndromes is pain. The affected structures in the shoulder can become trapped, leading to discomfort. The entrapment may have both structural and functional causes (Garving&et al.,2017).

Subacromial and subcoracoid impingement are the primary types of external impingement. Secondary extrinsic impingement occurs when there is glenohumeral instability without stenosis of the rotator cuff tendons in the subacromial or subcoracoid space. Internal impingement, on the other hand, refers to intra-articular impingement involving the glenoid labrum. It is categorized based on the specific portion of the glenoid that is affected by the impingement process, namely, posterior-superior and anterior-superior impingements (Escamilla, Hooks&Wilk,2009;Mulyadi&et al.,2009).

Shoulder impingement syndromes can be evaluated using a range of diagnostic methods. Radiographs are helpful for assessing osseous abnormalities, such as degenerative changes, spurs, and erosive changes (Cone, Resnick&Danzig,1984). Ultrasound (US) is highly accurate in detecting rotator cuff tears and dynamic assessment of impingement (Collins&et al.,1987). MRI is useful for visualizing rotator cuff tendon tears and bursal inflammation (Morag&et al.,2006). Magnetic resonance arthrography (MRA) is the preferred technique for assessing labral injuries, SLAP tears, and partial-thickness rotator cuff tears (Rowan&et al.,2004).

Primary extrinsic impingement

Subacromial impingement

Subacromial impingement is the predominant type of shoulder impingement and primarily arises due to friction between the coracoacromial arch and the underlying supraspinatus tendon or subacromial bursa. This friction leads to the development of tendinopathy in the supraspinatus tendon and bursitis in the subacromial bursa.

Although subacromial impingement is more commonly observed in patients over the age of 50, it is not uncommon to see it in younger patients as well. Typically, patients present with anterior or lateral shoulder pain during movements such as abduction, external rotation, forward elevation, and internal rotation of the shoulder (Neer,1972). During a physical examination, the "impingement sign" is typically observed, characterized by pain during passive shoulder elevation . This can be further confirmed through the "impingement test" (Neer,1983).

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Subacromial impingement is primarily diagnosed based on clinical assessment, but imaging plays a crucial role in supporting the diagnosis and identifying possible causes and effects of impingement.Static imaging modalities such as MRI and radiographs occasionally depict reduced subacromial distance as indirect evidence. Imaging features play a crucial role in the evaluation of subacromial impingement. Acromial morphology, which refers to the shape and appearance of the undersurface of the acromion, is a significant factor in the development of impingement. There are different classifications based on acromial morphology, including type 1 flat, type 2 concave, type 3 hooked, and type 4 inferiorly convex . Type 3 and type 2 acromion, particularly, are associated with a higher incidence and severity of cuff tears (Bigliani, Morrison&April,1986; Natsis&et al.,2007). Additionally, the presence of subacromial spurs is commonly observed in type 3 and type 2 acromion (Farley&et al., 1994). Another contributing factor is os acromiale, a condition where the acromial ossification centers fail to fuse by the age of 25, potentially leading to impingement (Hurst, Gregory&Reilly, 2019).

Degeneration of the acromioclavicular joint (ACJ) with inferior osteophytes can also contribute to narrowing of the supraspinatus outlet (Watson,1989). Additionally, a laterally or anteriorly downsloping acromion and a low-lying acromion can narrow the supraspinatus outlet (Edelson&Taitz, 1992). Table 1 summarizes subacromial impingement etiology. These findings can be identified through imaging studies.

Table 1 subacromial impingement etiology.

• Acromial shape Os acromiale Type III acromion Low lying acromion Downsloping lateral acromion Acromial spur
• Acromioclavicular joint degenerative disease
• Coracoacromial ligament ossification or thickening
• Shoulder instability
• Post-traumatic deformity
• Supraspinatus overdevelopment
• Chronic bursitis

On MRI, rotator cuff tendinosis and tears are typically observed at the anterior aspect of the supraspinatus tendon. Partial or full-thickness tears (figure 1) may be present in cases of subacromial impingement, with bursal-side partial-thickness tears being commonly encountered. The size, extent, and morphology of the rotator cuff tears, as well as the involvement of other tendons and the presence of muscle atrophy, are important considerations for treatment and prognosis (Seeger&et al.,1988). Imaging can also reveal significant subacromial-subdeltoid bursitis (figure 2), indicated by bursal fluid thickness greater than 3 mm, fluid medial to the ACJ, and fluid in the anterior aspect of the bursa (White, Schweitzer&Haims,2006).

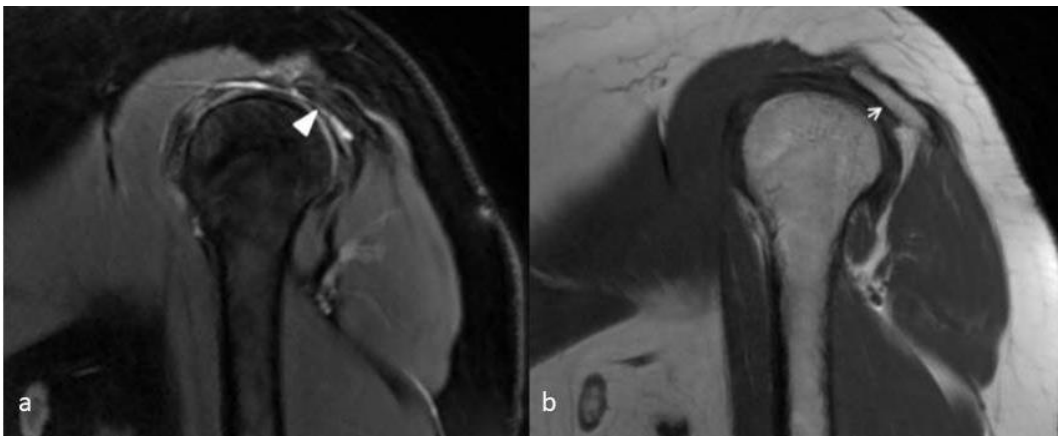

Figure 1: Sagittal proton density-weighted, fat-saturated, MR image (a) in a patient with subacromial impingement demonstrates full-thickness supraspinatus tear (white arrowhead), and sagittal T1-weighted, MR image (b) narrowing the subacromial space (white arrow).

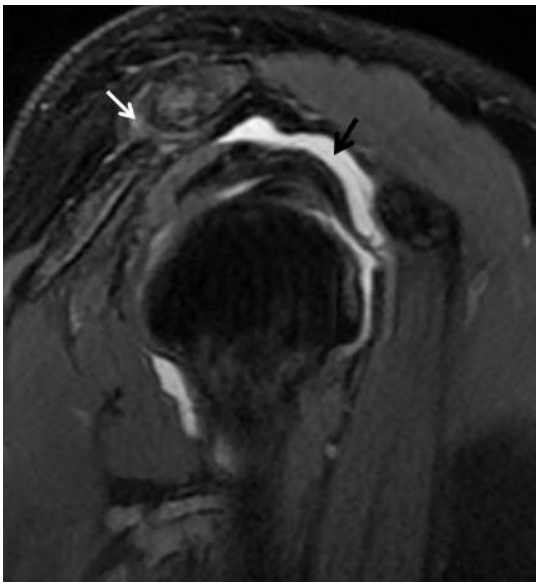

Figure 2: Sagittal proton density-weighted, fat-saturated, MR image in a patient presenting with clinical suspicion of subacromial impingement demonstrates ACJ degenerative changes (white arrow), and subacromial-subdeltoid bursitis (black arrow)

Subcoracoid impingement

Subcoracoid impingement, characterized by a narrowed coracohumeral interval, is an atypical form of shoulder impingement. Patients with this condition experience anterior shoulder pain specifically when their arm is adducted, internally rotated, and in forward flexion, commonly referred to as the military parade rest position . Palpation over the coracoid region reveals tenderness. Subscapularis tendon, long head of the biceps tendon, and middle glenohumeral ligament are the structures primarily affected in this condition (Giaroli&et al.,2006; Okoro, Reddy&Pimpelnarkar,2009).

The narrowing of the coracohumeral interval is often observed in individuals who have undergone previous rotator cuff repair, but it can also occur due to congenital factors or trauma (Giaroli&et al., 2006). Iatrogenic causes encompass a range of surgical procedures that can alter the relationship between the coracoid process and the lesser tuberosity or change the orientation of the coracoid or glenoid (Gerber, Terrier&Ganz,1985; Witten&et al.,2019). Congenital

factors include any anatomical variations that reduce the coracohumeral distance, such as an excessively long coracoid process or a protruding lesser tuberosity (Giaroli&et al., 2006). Fractures affecting the glenoid neck, coracoid process, or lesser tuberosity can also diminish the coracohumeral distance (Paulson, Watnik&Dines,2001).

On axial MRI images, the coracohumeral distance is measured as the shortest interval between the cortical margin of the coracoid and the cortical margin of the humeral head (Richards, Burkhart&Campbell,2005). Subcoracoid stenosis, defined as a coracohumeral interval less than 6 mm, demonstrates high specificity for subcoracoid impingement (Lo&Burkhart,2003). The identification of a narrow coracohumeral interval and the presence of subscapularis tendinosis or tears (figure3) on MRI can influence further management by alerting the clinician to the possibility of subcoracoid impingement, which may not have been initially recognized (Giaroli&et al.,2006).

Since subcoracoid impingement is known to cause persistent shoulder pain following supraspinatus repair (Suenaga, Minami&Kaneda, 2000), notifying the surgeon about the potential presence of subcoracoid impingement based on preoperative MRI findings can serve as a vital clue, leading to a comprehensive arthroscopic examination of the relationship between the subscapularis tendon and the coracoid. This examination may ultimately result in the decision to perform a subcoracoid decompression (Dines&et al.,1990; Patte,1990).

In addition to subscapularis tendinosis or tears, other MRI findings associated with subcoracoid impingement include subcoracoid bursal distension, cortical irregularities of the lesser tuberosity, and abnormalities of the long head of the biceps tendon (LHB) (Giaroli&et al.,2006). Ultrasound imaging may reveal pooling fluid in the subcoracoid bursa (Park& et al.,2018).

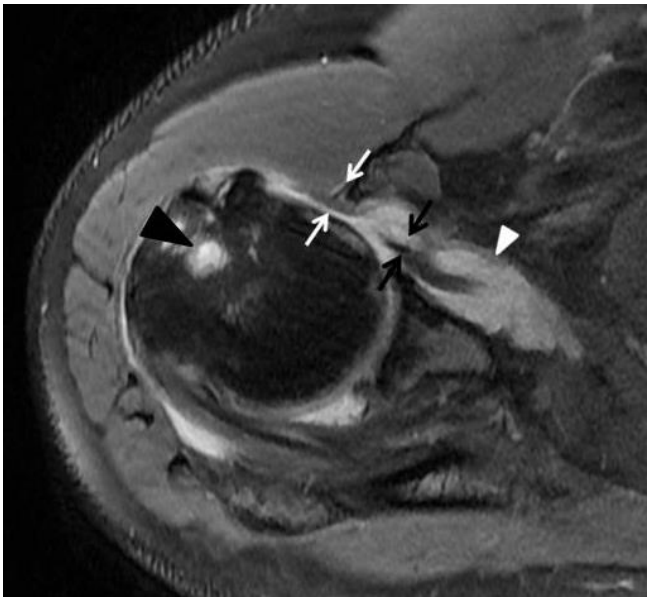

Figure 3: Axial proton density-weighted, fat-saturated MR image in a patient presenting with anterior shoulder pain demonstrates subcoracoid stenosis with coracohumeral interval of 5.5 mm (white arrows), and full-thickness supscapularis tear and tendon retraction (black arrows), degenerative subchondral cyst in the humeral head (black arrowhead) and a lax anterior capsular recess (white arrowheads).

Secondary extrinsic impingement

Secondary extrinsic impingement refers to impingement of the rotator cuff caused by glenohumeral instability (Jobe, Kvitne&Giangarra,1989). This condition is commonly

observed in individuals who engage in repetitive overhead or throwing activities and is the primary cause of impingement pain among athletes (Miniaci&Fowler,1993). The instability itself may not exhibit any symptoms initially and arises from the gradual stretching or laxity of the anterior capsule over time. This instability places an increased burden on the rotator cuff, leading to cuff fatigue. Consequently, superior migration of the humeral head occurs, resulting in the narrowing of the supraspinatus outlet (Belling Sørensen&Jørgensen,2000).

The use of MR arthrography can contribute to further management decisions by identifying anterior capsular laxity and ruling out any anatomical factors that may cause primary extrinsic impingement (Tuite,2003).

Internal impingement

Posterosuperior impingement

Posterosuperior impingement (PSI), also known as internal impingement, is an infrequent type of shoulder impingement that primarily affects the infraspinatus tendon and the posterosuperior glenoid labrum. This condition occurs when the shoulder is in an abducted and externally rotated position, commonly known as the ABER position (Giaroli, Major & Higgins,2005).

Patients experiencing posterosuperior impingement typically present with posterior shoulder pain and instability. It predominantly affects athletes who regularly put their shoulders through extreme abduction and external rotation, such as throwers, swimmers, volleyball players, and tennis players (Palmer&et al.,2020).

The repeated impingement of the infraspinatus tendon and the posterior portion of the supraspinatus tendon between the humeral head and the posterior superior rim of the glenoid occurs during extreme abduction and external rotation (ABER) movements. In these cases, extreme ABER leads to repetitive and excessive impact between the humeral head and the posterosuperior glenoid, trapping the posterior fibers of the supraspinatus tendon, anterior fibers of the infraspinatus tendon, and the posterosuperior labrum (Walch&et al.,1992; Jobe,1995). This leads to tendon degeneration, reactive cysts in the humeral head, and degeneration of the glenoid labrum (Giaroli&et al.,2006; Palmer&et al.,2020).

Radiographic and CT features associated with posterosuperior impingement include sclerosis and/or cysts in the greater tuberosity, osteochondral lesions in the posterior humeral head, remodeling of the posterior glenoid rim, and Bennett lesions. MRI and MR arthroscopy reveal articular-sided tears in the posterior supraspinatus and anterior infraspinatus tendons, posterosuperior labral tears or fraying (including type IIB SLAP tears), and humeral head cysts beneath the infraspinatus tendon (figure 4). Additional features may include anterior capsule laxity and posterior capsule thickening (Mistry & Campbell,2015; Chambers&Altchek,2013; Corpus &et al.,2016).

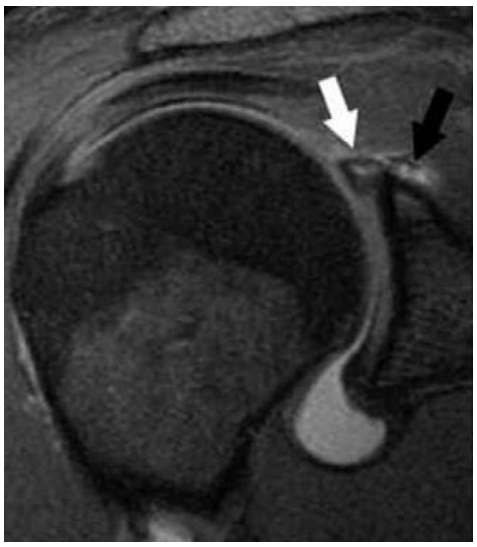

Figure 4: Coronal, T2-weighted, fat-saturated MRA image in a patient with PSI demonstrates a SLAP lesion (white arrow) with associated paralabral cyst (black arrow), (Mulyadi&et al.,2009).

Anterosuperior impingement

Anterior-superior impingement (ASI) is a less frequently discussed type of shoulder impingement, mainly due to its lower prevalence. It occurs when the rotator cuff, specifically the subscapularis tendon, gets compressed between the humeral head and the anterior-superior glenoid (Grainger,2008; Buss,Freehill&Marra,2009).

ASI is characterized by pain that arises during the follow-through phase, which involves horizontal adduction and internal rotation of the arm. ASI was identified as a form of intra-articular impingement responsible for anterior shoulder pain that couldn't be explained by other causes. ASI primarily affects individuals in the age group of 35-45 years and typically affects the dominant arm. Regular overhead activities during daily work, such as bricklaying or carpentry, as well as sports like swimming and tennis, have been associated with ASI(Gerber&Sebesta,2000; Habermeyer&et al.,2004; Struhl,2002).

The pulley system comprising the CHL, SGHL, anterior supraspinatus tendon, and superior subscapularis tendon insertion at the bicipital groove maintains the stability of the long head of the biceps (LHB) during shoulder movements (Lee&et al.,2007; Morag&et al.,2005; Krief,2005). ASI occurs when the pulley system and the articular surface of the subscapularis tendon impinge against the anterosuperior glenoid, leading to friction injury during certain shoulder motions. Abnormal contact between the rotator cuff and the superior labrum occurs when a pulley lesion and partial articular-sided subscapularis tendon tear are present (Gerber&Sebesta,2000; Habermeyer &et al., 2004; Struhl,2002). Trauma or degenerative changes can cause pulley lesions, such as falls with external rotation or sudden stops in overhead throwing (Gerber&Sebesta,2000). A pulley lesion disrupts the LHB's anterior stabilization of the glenohumeral joint, resulting in anterosuperior humeral translation during arm rotation (Walch &et al.,1998). ASI is further aggravated when a subscapularis tendon tear or an articular-sided anterior supraspinatus tendon tear coexist.

The presence of various lesions associated with ASI, such as subscapularis tears involving the deep surface insertion, tears of the SGHLe CHL complex, LHB subluxation (figure 5), and superior labral tears, can be visualized using conventional MRI or MR arthrography. Signs indicating the existence of a pulley lesion on MR arthrography encompass irregularities in the upper border of the subscapularis tendon, collection of contrast medium outside the joint, and subluxation of the LHB tendon (Lee&et al.,2007; Morag&et al.,2005; Krief,2005). These

abnormalities within the rotator interval are not exclusive to ASI, as the diagnosis primarily relies on clinical evaluation. Nonetheless, due to the potential confusion between ASI and subacromial impingement in clinical practice, MRI can assist in guiding appropriate management. In cases where patients have a history of chronic anterior shoulder pain and exhibit the range of aforementioned lesions, along with the absence of typical imaging features associated with external subacromial impingement, radiologists may suggest ASI as a potential cause for these findings in the report.

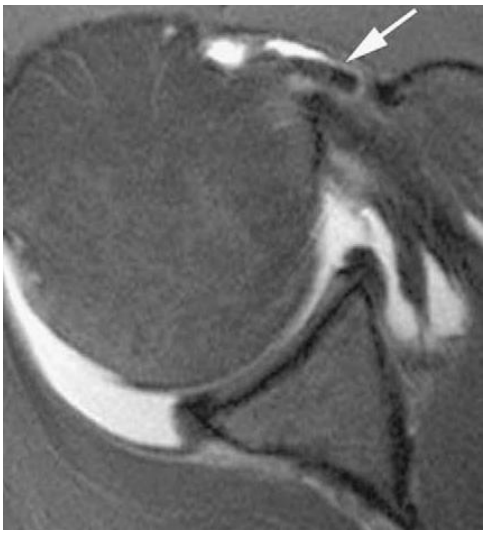

Figure 5: Axial, proton density-weighted, fat-saturated MR arthrographic imag in a patient with ASI demonstrates medial subluxation of LHB (white arrow),(Mulyadi&et al.,2009).

Summary

Shoulder impingement syndromes are frequently encountered and can be a primary cause of shoulder pain. They can occur in isolation or in conjunction with other shoulder pathologies. Understanding the relevant anatomy, causes, and clinical features is essential for accurate diagnosis and appropriate management. Imaging plays a crucial role in identifying key features and guiding clinical decisions related to shoulder impingement.

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Decoding Hpv: Epidemiology, Disease Associations, And The Role Of Vaccination

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A. Microbiology of HPV: Unraveling the Intricacies

The Replication Cycle of Human Papillomavirus

Natural History of HPV: A Deep Dive

Understanding the natural history of HPV infection is fundamental for developing and applying effective prevention strategies. The natural history of HPV infection includes the initial exposure, acute infection, latency, and possible reactivation. HPV can be transmitted through direct skin-to-skin or mucosa-to-mucosa contact, predominantly sexual contact (Burchell, Winer, de Sanjosé, & Franco, 2006).

Following the initial exposure, the virus establishes an acute infection, during which it can be transmitted to others. Most HPV infections are asymptomatic and transient, with the majority being cleared or suppressed below detectable levels by the immune system within 1-2 years of initial infection. However, in some cases, HPV can persist, particularly high-risk types, leading to the development of precancerous lesions and, ultimately, invasive cancer (Rodríguez, Schiffman, Herrero, Wacholder, Hildesheim, & Castle, et al., 2010).

Latent HPV infection, in which the virus remains in the body in an inactive state, can be reactivated, particularly in immunosuppressed individuals. Risk factors for reactivation include age, hormonal changes, immune status, and coinfections (Woodman et al., 2007).

HPV Affiliation with Different Anatomical Sites: Cutaneous, Anogenital Epithelium, and Other Mucosal Surfaces

HPV has an affinity for different types of epithelial tissues. Cutaneous HPV types, primarily from the beta and gamma genera, infect the skin and are associated with non-melanoma skin cancer and cutaneous warts (de Villiers, Fauquet, Broker, Bernard, & zur Hausen, 2004). Certain HPV types, particularly types 1 and 2, can cause common warts, whereas others can cause plantar and flat warts.

HPV can also infect anogenital epithelium and other mucosal surfaces. High-risk mucosal HPV types, including types 16 and 18, are the primary causes of cervical cancer, with HPV 16 being the most prevalent. Other cancers associated with these HPV types include vulvar, vaginal, penile, anal, and oropharyngeal cancers (Bouvard, Baan, Straif, Grosse, Secretan, & Ghissassi, et al., 2009). These mucosal HPV types can cause anogenital warts and recurrent respiratory papillomatosis.

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HPV can also infect the oropharynx, particularly the base of the tongue and tonsils, resulting in oropharyngeal cancer. The incidence of HPV-positive oropharyngeal cancer has increased steadily, particularly in developed countries. This rise in incidence has been attributed to changes in sexual behavior, including increased oral sexual practices (Chaturvedi, Engels, Pfeiffer, Hernandez, Xiao, & Kim, et al., 2011).

The broad tissue tropism of HPV contributes to its diverse clinical manifestations, ranging from benign lesions such as warts and papillomas to malignant tumours. Specific HPV types and host factors determine the clinical outcomes of the infection.

B. Historical Perspective of HPV Infections

The history of HPV and its association with human diseases has been complex and tapestry unfolding over many decades. The first direct evidence of HPV-causing human disease emerged in the early 20th century when Ciuffo (1907) discovered a contagious agent responsible for warts (Ciuffo, 1907). It was not until the mid-20th century that the Pap smear, developed by George Papanicolaou, revolutionised the detection of cervical cancer, paving the way for an understanding of the relationship between persistent viral infection and carcinogenesis (Papanicolaou & Traut, 1941).

The term "papillomavirus" was first used in 1930 to refer to papillomas (warts) caused by the virus (Rous & Beard, 1935). However, the association between HPV and cervical cancer remained obscure until the 1980s, when Zur Hausen postulated and later confirmed the presence of HPV DNA in cervical cancer tissues, earning him the Nobel Prize in Physiology and Medicine in 2008 (Zur Hausen, 2002).

The first HPV types, HPV types 1 and 2, were cloned in 1980. Since then, more than 200 HPV types have been identified and fully sequenced (de Villiers, 2013). The development of molecular techniques has facilitated the identification and classification of various types of HPV. It helped to establish a causal relationship between high-risk HPV types and various cancers, including cervical, anogenital, and oropharyngeal cancers (Munoz, Bosch, & de Sanjosé, 2003).

The late 20th and early 21st centuries have witnessed significant advancements in HPV research and the development of preventive measures. The first prophylactic HPV vaccines were approved in the mid-2000s and have demonstrated high efficacy in preventing infections with high-risk HPV types (Harper, Franco, & Wheeler, 2006). HPV vaccination programs have been implemented worldwide, significantly reducing the incidence of HPV-associated diseases and transforming our approach to prevention.

C. Epidemiology of Anogenital HPV Infections: A Global Scenario
The Influence of HPV Vaccination on Anogenital Infections

The introduction of HPV vaccines in the mid-2000s significantly transformed the landscape of anogenital HPV infection (Garland et al., 2007). Vaccines targeting high-risk HPV types 16 and 18 have demonstrated high efficacy in preventing new infections, reducing the prevalence of these types, and ultimately decreasing the incidence of HPV-associated diseases including anogenital warts and precancerous cervical lesions (Drolet et al., 2015).

The impact of HPV vaccination is most notable in countries with a high vaccine coverage. For instance, Australia, which implemented a nationwide HPV vaccination program in 2007, observed a significant decline in the incidence of anogenital warts and high-grade cervical abnormalities among the vaccinated age groups (Brotherton et al., 2011; Ali et al., 2013). Similarly, other countries with robust vaccination programs have reported reductions in HPV-

related outcomes, highlighting the effectiveness of vaccination as a public health strategy for controlling HPV infections (Baldur-Felskov et al., 2014; Lehtinen et al., 2017).

The Gendered Impact: Females and Genital Infections

HPV infections and their associated diseases profoundly affect women's health worldwide. Nearly all cases of cervical cancer, the fourth most common cancer in women globally, are attributable to HPV, with HPV types 16 and 18 being the most prevalent types (Brisson et al., 2019).

In addition to cervical cancer, HPV is responsible for a significant proportion of anogenital cancers in women, including vulvar and vaginal cancer (de Sanjose et al., 2010). Furthermore, low-risk HPV types, primarily types 6 and 11, cause a substantial burden on anogenital warts, which, although not life-threatening, can cause significant psychosocial distress and economic costs (Patel et al., 2013).

Women in their late teens and early 20s are most susceptible to HPV infection, with a decrease in prevalence after the age of 30 years. However, a second peak in HPV prevalence has been observed in some postmenopausal women, likely reflecting new infections or reactivation of latent infections (Castle et al., 2005).

Anogenital HPV Infections: A Worldwide View

HPV infections, particularly those affecting anogenital regions, are a significant global health concern. An estimated 291 million women worldwide are carriers of HPV DNA, indicating active infection (Bruni et al., 2010). The prevalence of HPV varies widely by region, reflecting differences in sexual behavior, circumcision prevalence, and HPV vaccination coverage (Forman et al., 2012).

High-risk HPV types are most prevalent in sub-Saharan Africa, Latin America, and the Caribbean, whereas low-risk HPV types are most common in North America and Europe (Bruni et al., 2010). Despite these regional variations, HPV 16 remains the most prevalent HPV type globally, followed by HPV 18, which is included in the current HPV vaccines (Clifford et al., 2005).

The burden of HPV-associated diseases, including anogenital cancer and warts, varies regionally. However, it is overwhelmingly high in low-income and middle-income countries, which account for over 80% of the global burden of cervical cancer, owing to limited access to HPV vaccination and cervical screening services (Arbyn et al., 2020).

The epidemiology of anogenital HPV infections underscores the importance of preventive measures, including HPV vaccination and regular cervical screening, for controlling the global burden of HPV-associated diseases.

D. Associations Between HPV and Diseases: An Expansive Review

HPV-related Diseases in Females: From Cervical to Vulvar and Vaginal Cancer

HPV has been strongly implicated in the pathogenesis of various cancers affecting the female reproductive system. The most well-known among these is cervical cancer, with HPV DNA found in nearly all cases (Walboomers et al., 1999). High-risk HPV types, particularly types 16 and 18, are frequently associated with cervical cancer, contributing to over 70% of the cases worldwide (de Sanjosé et al., 2010). Persistent infection with high-risk HPV types is recognized as a necessary cause of cervical cancer, and the progression from infection to cancer

involves a series of genetic and epigenetic changes facilitated by viral oncoproteins E6 and E7 (Moody & Laimins, 2010).

In addition to cervical cancer, HPV has been implicated in other anogenital cancers in women, including vulvar and vaginal cancers. High-risk HPV types are found in approximately 40% of vulvar cancers and 70% of vaginal cancers, with HPV 16 being the most common type (de Sanjosé et al., 2010). The pathogenesis of these cancers is similar to that of cervical cancer, with persistent HPV infection leading to precancerous lesions, which may progress to invasive cancers.

HPV Influence Across Genders: Nongenital Warts, Genital Warts, and More

HPV infections are not restricted to the anogenital region and can affect various other sites in both females and males. One of the most common manifestations of HPV infection is skin warts, or cutaneous warts, caused by low-risk HPV types such as HPV 1, 2, and 4 (Bruggink et al., 2012). Cutaneous warts often resolve spontaneously but can persist and recur in some individuals.

Genital warts, primarily caused by low-risk HPV types 6 and 11, are common sexually transmitted conditions in both females and males (Patel et al., 2013). Genital warts can cause significant psychosocial distress and are challenging to manage owing to their recurrent nature.

Moreover, HPV has been associated with other diseases affecting both sexes, including conjunctival papillomas and certain types of skin cancer, although the risk is generally higher in immunocompromised individuals (Gross et al. 2017).

HPV and its Association with Anal Cancer

HPV is a major risk factor for anal cancer, which is a relatively rare but increasingly common malignancy. High-risk HPV types, particularly HPV 16, are found in over 80% of anal cancer cases, suggesting a critical role in the pathogenesis of this cancer (Hoots et al., 2009). Both females and males are affected, but the incidence is notably higher in men who have sex with men, especially those living with HIV (Machalek et al., 2012).

The development of anal cancer involves the progression from HPV infection to high-grade anal intraepithelial neoplasia, a precancerous condition, and eventually to invasive cancer. This progression is facilitated by persistent infection with high-risk HPV types and is likely influenced by other factors such as immune status and co-infection with other sexually transmitted infections (Moscicki et al., 2015).

The Link Between HPV and Oropharyngeal Cancer

In recent years, there has been growing recognition of the role of HPV in oropharyngeal cancer, a subset of head and neck cancers. HPV is estimated to contribute to approximately 70% of oropharyngeal cancer cases in the United States and other developed countries, with HPV 16 being the most prevalent type (Chaturvedi et al., 2011). HPV-positive oropharyngeal cancer has distinctive clinical and molecular characteristics and is associated with better prognosis than HPV-negative cancer (Ang et al., 2010).

HPV transmission to the oropharynx is believed to occur via oral sex, although other modes of transmission may also play a role (D'Souza et al., 2007). The incidence of HPV-associated oropharyngeal cancer has increased over the past few decades, particularly among men, making this an important area of ongoing research (Chaturvedi et al., 2013).

Recurrent Respiratory Papillomatosis: A Consequence of HPV

Recurrent respiratory papillomatosis (RRP) is a rare, but potentially serious condition caused by HPV, specifically HPV types 6 and 11. RRP is characterized by the growth of benign tumors in the respiratory tract that can cause voice changes and breathing difficulties (Fortes et al., 2012). This condition can occur in both children (juvenile-onset RRP) and adults (adult-onset RRP), and has different implications for disease management and prognosis.

The exact mechanism of HPV transmission leading to RRP is not fully understood, but maternal-neonatal transmission during childbirth has been proposed for juvenile-onset RRP (Fortes et al., 2012). Despite its benign nature, RRP can significantly impact quality of life due to the recurrent nature of the disease and the potential for airway obstruction.

Other Cutaneous Diseases Triggered by HPV

In addition to warts and cancers, HPV infection is associated with several other cutaneous conditions. Epidermodysplasia verruciformis (EV) is a rare genodermatosis associated with specific types of HPV (primarily HPV 5 and 8) that predisposes individuals to widespread cutaneous warts and increases the risk of non-melanoma skin cancers (Orth, 2006). EV pathogenesis involves an abnormal immune response to HPV, often during childhood or adolescence.

HPV has also been implicated in a subset of non-melanoma skin cancers including squamous and basal cell carcinomas, particularly in immunocompromised individuals (Gross et al. 2017). HPV may act as a co-carcinogen, enhancing the carcinogenic effects of UV radiation, although the exact role of HPV in these cancers remains unclear.

E. Risk Factors for HPV Infection: A Comprehensive Overview

Human papillomavirus (HPV) infection is the most common sexually transmitted infection worldwide, affecting a significant proportion of sexually active men and women at some point in their lives. Understanding the risk factors of HPV infection is crucial for developing effective preventive strategies. This section reviews the diverse range of factors associated with an increased risk of HPV infection.

Sexual Behavior

Sexual behavior is one of the most well-established risk factors for HPV infection. Individuals who engage in sexual activity at a young age, have multiple sexual partners, or have a partner with multiple past or concurrent partners are at a higher risk for HPV infection (Burchell et al., 2006). Moreover, certain sexual behaviors, such as unprotected and anal sex, have been associated with an increased risk of HPV infection and related diseases (Giuliano et al., 2011).

Gender and Age

Sex and age can also influence the risk of HPV infection. Females tend to acquire HPV shortly after sexual debut and have a high prevalence of infection in their late teens and early 20s (Dunne et al., 2007). In contrast, the prevalence of HPV infection in males remains relatively stable across age groups, reflecting ongoing virus acquisition and transmission (Giuliano et al., 2008).

Immunodeficiency

Individuals with an impaired immune system, whether due to conditions like HIV/AIDS or immunosuppressive treatment, are at a higher risk for HPV infection and related diseases

(Grulich et al., 2007). This is likely due to a decreased ability to clear the virus or to control its replication.

Smoking

Smoking has been consistently associated with an increased risk of HPV infection, persistence, and HPV-related diseases such as cervical cancer (Plummer et al., 2003). This may be due to the immunosuppressive effects of smoking or direct carcinogenic effects of tobacco byproducts on the cervical epithelium.

Socioeconomic Factors

Socioeconomic factors, including low income and education level, have been associated with a higher risk of HPV infection and related diseases (Parikh et al., 2003). These factors may influence HPV risk indirectly through their impact on access to healthcare, sexual behavior, and other risk behaviors.

Other Factors

Other factors that have been associated with an increased risk of HPV infection include the long-term use of oral contraceptives, high parity (i.e., having many children), and co-infection with other sexually transmitted infections (STIs), such as Chlamydia trachomatis (Smith et al., 2003; Vaccarella et al., 2006; Samoff et al., 2005).

In conclusion, the risk of HPV infection is influenced by a complex interplay of behavioral, biological, and socioeconomic factors. Understanding these risk factors is crucial for developing targeted interventions to reduce the burden of HPV infection and related diseases.

F. HPV Vaccination: The Game Changer in HPV Epidemic

History of HPV Vaccine: A Revolutionary Timeline

The history of HPV vaccination is a revolutionary timeline that has marked a paradigm shift in the fight against HPV-related diseases. The development of the first HPV vaccine was fueled by the identification of HPV as the primary cause of cervical cancer in the 1980s by Harald Zur Hausen, who earned him a Nobel Prize in Medicine in 2008 (Zur Hausen, 2002). The development of technology has led to the production of virus-like particles (VLPs) that mimic the structure of HPV, but do not contain any viral DNA, making them non-infectious and ideal vaccine candidates (Kirnbauer et al., 1992).

In 2006, the U.S. The Food and Drug Administration (FDA) approved the first HPV vaccine, Gardasil, a quadrivalent vaccine designed to protect against HPV types 6, 11, 16, and 18. This is a milestone in cancer prevention, as types 16 and 18 are responsible for approximately 70% of all cervical cancers worldwide, whereas types 6 and 11 account for most genital warts (Munoz et al., 2003).

In 2009, the FDA approved the second HPV vaccine, Cervarix, a bivalent vaccine targeting HPV types 16 and 18. Gardasil 9, approved by the FDA in 2014, is the most recent addition to the arsenal against HPV. It protects against the same types of HPV as the original Gardasil and five other high-risk HPV types:31, 33, 45, 52, and 58 (FDA, 2014).

Available HPV Vaccines: Current Landscape and Future Prospects

Three vaccines that vary in the number of HPV types targeted have been clinically developed.

1. Human papillomavirus quadrivalent vaccine (Gardasil) targets HPV types 6, 11, 16, and 18.

2. Human papillomavirus 9-valent vaccine (Gardasil 9) targets the same HPV types as the quadrivalent vaccine (6, 11, 16, and 18), and types 31, 33, 45, 52, and 58.

3. Human papillomavirus bivalent vaccine (Cervarix) targets HPV types 16 and 18 (Markowitz et al., 2014).

The choice of vaccine depends on the local availability, cost, and specific population needs. In the United States, only a 9-valent vaccine is currently available. The rationale for using the 9-valent vaccine is its broader HPV-type coverage, which further reduces the risk of cervical cancer and other HPV-related diseases in both males and females. All these vaccines are prophylactic and designed to prevent initial HPV infection and subsequent HPV-associated lesions.

The future of HPV vaccination is to improve vaccine coverage and to develop next-generation vaccines. Efforts are ongoing to develop pan-HPV vaccines that can provide protection against nearly all HPV types. Moreover, therapeutic vaccines designed to treat existing HPV-associated lesions are currently in the pipeline but are not yet clinically available (Einstein et al., 2021).

The advent of HPV vaccination has been a game-changer in the fight against HPV. However, the full potential of these vaccines can only be realized through comprehensive and equitable vaccine coverage worldwide.

Rationale for HPV Vaccination

The primary rationale behind the development and deployment of HPV vaccines is the prevention of HPV-related diseases including cervical cancer, other anogenital cancers, oropharyngeal cancer, and genital warts. Given the high prevalence of HPV infections and their association with numerous diseases, widespread vaccination can significantly reduce the global burden of HPV-related diseases.

HPV types 16 and 18, which are targeted by all three HPV vaccines, account for approximately 70% of all cervical cancer cases worldwide. The additional types targeted by the 9-valent vaccine (types 31, 33, 45, 52, and 58) are responsible for 20% of cervical cancer cases (Joura et al., 2015). Vaccination with quadrivalent or 9-valent HPV vaccines also protects against anogenital warts, which are primarily caused by HPV types 6 and 11, and represent a significant cause of morbidity (Smith et al. 2007).

Modeling studies have indicated that HPV vaccination is cost-effective within the recommended age range. For instance, one study suggested that vaccination of the entire United States population of 12-year-old girls would annually prevent more than 200,000 HPV infections, 100,000 abnormal cervical cytology examinations, and 3300 cases of cervical cancer, assuming that cervical cancer screening continues as recommended (Kim et al., 2007).

Administration of HPV Vaccines

According to the Advisory Committee on Immunization Practices (ACIP), routine HPV vaccination is recommended for all females and males within a specific age range. Specifically, routine HPV vaccination is recommended at ages 11–12 years, but it can be administered starting at 9 years of age. For adolescents and adults aged 13–26 years who have not been

previously vaccinated or have not completed the vaccine series, catch-up vaccination is recommended (Meites et al., 2019).

Although catch-up vaccination is not routinely recommended for adults aged ≥ 27 years, the decision to vaccinate people in this age group should be made individually. For some individuals in this age group, such as those with no prior sexual experience or limited number of prior sexual partners, the risk of prior HPV exposure may be very low. In such cases, HPV vaccination may be beneficial if it poses the risk of HPV exposure.

Ideally, HPV immunization should occur prior to an individual's sexual debut, as clinical trial data suggest that immunization with the HPV vaccine is most effective among individuals who have not been infected with HPV (patients who are "HPV-naïve"). However, sexually active individuals should be vaccinated, which is consistent with age-specific recommendations.

Regarding vaccine choice, the 9-valent vaccine is generally recommended if cost and availability are not an issue because of its greater HPV-type coverage. The same formulation should be used to complete the series if possible. However, if the initial HPV vaccine formulation is unknown or unavailable, a different HPV vaccine formulation can be used to complete the series.

To Summarize:

Chapter Summary: Human Papillomavirus (HPV): An Unseen Enemy

This chapter explores Human Papillomavirus (HPV), a ubiquitous and significant pathogen implicated in various diseases, including several types of cancers. This chapter is organized into six major sections.

1. This chapter begins with a detailed analysis of the microbiology of HPV and discusses the virus's replication cycle and its natural history. It further explored the virus's affiliation with anatomical sites, highlighting its predilection for cutaneous, anogenital epithelium, and other mucosal surfaces.

2. The historical perspective of HPV infections is then discussed, offering a retrospective look at the evolving understanding of the virus and its implications in the scientific and medical communities.

3. This chapter presents a global view of the epidemiology of anogenital HPV infection. It discusses the influence of HPV vaccination on anogenital infections, the gendered impact of the virus, and the worldwide distribution of anogenital HPV infections.

4. This chapter extensively reviews the association between HPV and various diseases. It covers HPV-related diseases in females, such as cervical, vulvar, and vaginal cancer; the influence of the virus across sexes; and its association with anal and oropharyngeal cancer, recurrent respiratory papillomatosis, and other cutaneous diseases triggered by HPV.

5. The fifth section outlines the risk factors for HPV infection and provides a comprehensive overview of the sexual and non-sexual factors that increase susceptibility to the virus.

6. The final section explores HPV vaccination as a game-changer in the HPV epidemic. It traces the history of HPV vaccines, discusses currently available vaccines and their applications, and details their administration guidelines.

This chapter offers a robust and detailed examination of HPV, from its microbiology to its association with various diseases, risk factors, and vaccination's crucial role in controlling

its spread. It serves as a valuable resource for understanding the complexities of HPV and the strategies employed to manage its impact on global health.

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Investigation Effect Of Some Environmental Factors And Timing Of Artificial Insemination On Milk Yield In Holstein Cows*

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Introduction

Maintenance and profit on a dairy cow farm are dependent on high-yielding animals and effective herd management. The amount of milk produced by these cows during their lifetime, as well as their contribution to the farm, are used to assess them. As a consequence, these farms monitor herd and animal production regularly, as well as current positive and negative environmental factors. Dairy cow breeding is a success on the majority of Turkish farms (Cak & Yilmaz 2015). Lactation performance in dairy cattle is regulated by genetic and environmental variables. Milk development, lactation time, and dry period have all been shown to be influenced by genetic history, environment, illnesses, food, calving year, and season. Productivity is affected by breed, era, lactation time, parity, and milking frequency (Msanga et al 2000; Epaphras Karimuribo & Msellem et al 2004). Holstein cows were once thought to be the world's most dairy cows (M'hamdi et al 2012). The reproductive productivity of the dairy cow is crucial to the dairy enterprise's financial viability. Artificial insemination (AI) is a vital reproductive technology in the dairy industry. AI minimizes the occurrence of sexually transmitted diseases in cattle while simultaneously enhancing the use of genetically superior sires to improve herd performance (Hagevoort & Garcia 2013).

Estrus identification and AI are the most expensive procedures in many dairy farms. Correct estrus identification is connected to extended calving cycles, milk loss, increased veterinary expenditures, increased heifer breeding costs, and slower genetic development (Anonymus 2017).

It is critical to precisely identify cows to be inseminated in order for them to become pregnant, calve, and return to peak milk production, as well as to generate a steady supply of replacements (Roelofs et al 2010). Many approaches for predicting estrus have been tried, and automatic behavior tracking is one of the methods that has been implemented by producers and is proving to be useful (Fricke et al 2014; LeRoy 2016).

For more than 70 years, scientists have studied the timing of insemination in relation to the first symptom of estrus. The "a.m.-p.m. rule" indicated that if a cow was seen in standing estrus in the morning, AI should take place that day, and if a cow was seen in estrus in the afternoon, AI should take place the next morning (LeRoy 2016). For over a century, researchers have researched the effect of artificial insemination timing on the sex ratio of cow progeny (Ericsson & Ericsson 1998). Many contradictory results have been reported in the last decade about the

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influence of artificial insemination timing on the sex ratio of progeny in cows (Rorie 1999; Martinez et al 2004). The purpose of this study was to look into the influence of several environmental conditions and the timing of artificial insemination on milk output in Holstein cows.

Materials and Methods

Location

The farm where we received the data in our work; It is a dairy farm located in the Mediterranean Region of Turkey, Kadirli District of Osmaniye Province (37°, 22'28.1 North, 36°, 05'51.3 East). The district is at an altitude of 96 m, with an average annual maximum temperature of 36°C in August and a minimum temperature of 3°C in January, with an average annual rain of 890 mm3 (MGM 2017).

Animal Materials

This study was conducted on healthy Holstein cows (parity ranging from 1 to 6) at an Osmaniye dairy farm during a 5-year period. Cows were kept in free-stall barns and fed a total mixed ration (TMR) of corn silage, alfalfa hay, concentrate, and mineral mix twice daily. They had free access to water. Using an automated milking system, cows were milked twice a day at about 12-hour intervals, and the average lactation milk output was 9042 kg per lactation.

Methods

Milk Yield Traits

Data were obtained from Holstein cows housed on a commercial dairy farm in Osmaniye between December 2010 and February 2014. Individual cow milk outputs were recorded twice a day at each milking and preserved as daily milk yields (kg). Each cow's average daily milk output was determined. A total of 91 cow's lactation records and 60 cow's dry period records were included in the analysis. Since 31 cows were in the first lactation period, dry periods were not calculated.

Estrus and AI

Estrus was seen by two experienced herders three times each day (at 08:00, 16:00, and 24:00), with each observation lasting around 30 minutes. When the cows stood to be mounted, the beginning of estrus was determined. Two veterinarian technicians used normal cattle methods to perform artificial inseminations. The cows were inseminated with frozen-thawed sperm 0-12 h (Group 1) and 13-24 h (Group 2) after the beginning of estrus was identified.

Statistical Analysis

SPSS (2013) was used to examine the data. Duncan and chi-squared tests were used to examine the effects of environmental conditions and artificial insemination timing on milk output in Holstein cows.

Results

Least square means for milk yield traits are presented in Table 1. The effects of calving year on lactation period, lactation milk yield, 305-day milk yield, and ME-305-day milk yield were significant ($p<0.001$). Effects of lactation number on ME-305 days milk yield were significant ($p<0.05$). Effects of AI Time on ME-305 days milk yield were significant ($p<0.01$).

The average of lactation length, lactation milk yield, 305 days milk yield, ME-305 days milk yield and dry period (Table 2) was estimated as 372,3 day, 9042,4 kg, 8146,2 kg, 9051,8 and 54,0 day respectively; milk yields at 305 days were lowest in 2010, at 6210,1 kg, and greatest in 2013, at 9462,8 kg. Milk yields were lowest in 4 years of age at 7834,2 kg and greatest in 6 years and older at 8620,8 kg during 305 days. Furthermore, the greatest 305-day milk yield in cows calving in the summer was 8539,3 kg, while the lowest amount in animals calving in the spring was 7948,5 kg.

Lactation length was shortest in 2014 at 314,9 days and longest in 2013 at 411,3 days. Lactation length was longest in 4 and over lactation at 383,5 days and shortest in 2nd lactation at 356,4 days.

Table 1. Least Squares Means, Significance and Multiple Comparison Test Results Belong to Milk Production Traits.

Factors	n	Lactation length (day)	Lactation milk yield (kg)	305 days milk yield (kg)	ME-305 days milk yield (kg)
		$\bar{X} \pm S\bar{x}$	$\bar{X} \pm S\bar{x}$	$\bar{X} \pm S\bar{x}$	$\bar{X} \pm S\bar{x}$
General mean	91	372,3±8,97	9042,4±287,02	8146,2±214,89	9051,8±253,12
Calving year		***	***	***	***
2010	11	326,5±11,33^{c}	6625,4±251,51^{c}	6210,1±155,79^{d}	7030,9±268,11^{c}
2011	13	348,8±27,74^{bc}	7487,2±613,85^{bc}	6938,4±419,16^{cd}	7701,1±500,22^{bc}
2012	19	392,5±23,00^{ab}	8635,3±568,32^{b}	7720,4±416,37^{bc}	8603,2±541,90^{bc}
2013	33	411,3±13,94^{a}	10866,7±502,41^{a}	9462,8±388,37^{a}	10452,4±461,00^{a}
2014	15	314,9±8,91^{c}	8665,0±317,31^{b}	8255,8±201,71^{ab}	9191,1±271,25^{ab}
Lactation No.		NS	NS	NS	*
1. Lactation	31	374,5±15,73	8753,7±484,74	7894,0±365,46	9939,5±475,29^{a}
2. Lactation	21	356,4±18,46	8945,7±536,11	8185,5±388,47	9163,1±436,93^{ab}
3. Lactation	11	368,0±22,67	8684,4±891,45	7790,8±670,52	8127,4±726,99^{b}
4. and over Lactation	28	383,5±17,08	9575,3±558,62	8534,5±420,31	8348,5±412,11^{b}
Calving season		NS	NS	NS	NS
Autumn	15	359,9±17,74	9049,6±704,39	8135,6±505,84	9076,0±658,93
Winter	39	360,2±14,55	8684,1±414,75	7959,2±308,10	9117,3±389,02
Spring	12	377,3±23,23	8835,4±729,20	7948,5±564,39	8835,3±670,29
Summer	25	396,2±17,58	9696,4±618,01	8539,3±476,18	9038,9±498,72
Calving age		NS	NS	NS	NS
2	30	377,0±16,05	8815,3±497,12	7927,9±376,31	10036,0±481,17
3	20	349,6±18,01	8849,4±554,46	8132,8±404,63	9159,3±459,34
4	13	372,3±22,23	8715,8±781,79	7834,2±579,00	8129,6±623,00
5	11	383,0±34,05	9346,9±955,10	8401,3±707,09	8301,8±699,36
6 and older	17	383,8±18,48	9723,0±703,48	8620,8±536,32	8378,8±523,54
Service Period		NS	NS	NS	NS
0-74 day	15	350,33±19,54	8613,47±678,88	7802,66±493,71	7949,87±503,06
75-100 day	7	341,71±24,30	8958,29±1041,02	8229,99±794,49	8577,14±772,11
101-125 day	4	416±53,58	10509,25±1862,54	9137,53±1400,87	10148,75±1604,80
126-150 day	5	392,00±51,14	9414,60±1588,32	8521,78±1216,62	8782,40±1130,72
151 and over	18	391,50±20,65	10050,28±583,98	8899,87±447,34	9103,00±449,71
AI Time		NS	NS	NS	**
0-12 hour	30	377,0±16,05	8815,3±497,12	7927,9±376,31	10036,0±481,17
13-24 hour	61	370,0±10,89	9154,1±353,52	8253,6±262,85	8567,7±276,57

*p<0.05; **p<0.01; ***p<0.001; NS: non-significant; a, b, c: Means without a common superscript within each variable and each factor differ (p<0.05), AI: Artificial Insemination.

Table 2. Least Squares Means, Significance and Multiple Comparison Test Results Belong to Dry Period, Day.

Factors	n	dry period (day)
		$\bar{X} \pm S\bar{x}$
General mean	60	54,0±0,93
Calving year		NS
2010	7	58,6±1,91
2011	8	53,1±2,50
2012	12	53,7±1,65
2013	22	52,8±1,72
2014	11	54,6±2,42
Lactation No.		NS
1. Lactation	-	-
2. Lactation	21	54,1± 1,69
3. Lactation	11	55,9 ± 1,66
4. and over Lactation	28	53,3 ± 1,41
Calving season		NS
Autumn	11	52,5 ± 1,66
Winter	20	54,3 ± 1,71
Spring	8	54,0 ± 1,91
Summer	21	54,6 ± 1,83
Calving age		NS
2	-	-
3	20	53,6± 1,68
4	12	56,7 ± 1,69
5	11	53,1 ± 2,53
6 and older	17	53,4 ± 1,71
Service Period (day)		NS
0-74	15	55,2±1,44
75-100	7	50,5±1,95
101-125	4	51,5±4,67
126-150	5	53,00±3,83
151 and over	18	52,7±1,84

NS: non-significant

In this study, multiple correspondence analysis was performed to visualize the effect of some factors on milk yield. The results are given in Table 3 and Figure 1.

Table 3. The results of Multiple Correspondence Analysis.

Model Summary			
Dimension	Cronbach's Alpha	Variance Accounted For	
		Total (Eigenvalue)	Inertia
1	0,838	4,203	0,382
2	0,811	3,802	0,346
Total		8,005	0,728
Mean	0,825[a]	4,003	0,364

a: Mean Cronbach's Alpha is based on the mean Eigenvalue.

As a result of the dimension reduction as seen in Table 3; the first dimension is 38.2% of the total variation, while the second dimension is 34.6%. Thus, the relationship between the properties is reduced to 2 dimensions and the total variation is 72.8%.

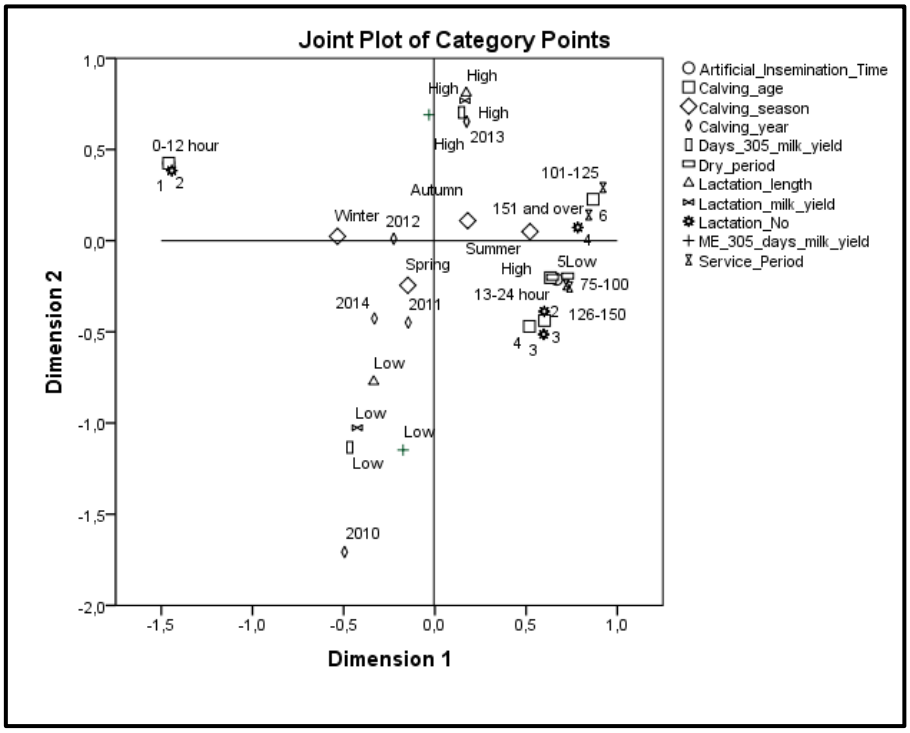

Figure 1. The graphic of Multiple Correspondence Analysis.

When the relations between the features are examined visually in Figure 1; the lactation milk yield in 2013 is high in animals that four-years old-calving cows, in autumn and summer-calving cows and service period more than 101 days-cows. On the other hand, in 2010-2012, in winter and spring seasons-calving cow's lactation milk yield is low.

When the relationships between the characteristics are examined according to the first dimension; the milk yield is low when insemination is made in the 0-12-hour period in the animals that 1-2 years old-calving. Also, insemination between 13-24 hours is positively related to high milk yield.

Discussion

In a dairy farm, fertility is also important if milk production is important. During the last fifty years passed, milk production in developed countries has greatly increased the milk yield

of cattle. But with this selection milk fertility has increased and fertility has decreased seriously. Several factors have been suggested in this regard. These are the causes, such as genetic, physiological, nutritional and managerial factors, which affect the fertile life of animals directly and indirectly.

While it is desirable to achieve high fertility in dairy farms, it is very important that the estrous is fixed at the right time. A 10% increase in the correct detection rate of oestrus time reduces the number of idle days from an average of 136 days to 119 days. In addition, the increase in correct estrus time detection rate increases the reproductive efficiency by shortening the two birth intervals. Estrus symptoms and the accurate determination of oestrus with these symptoms are very important for dairy farms, even though new methods have been developed (Daşkın 2005).

As known in dairy cattle, age and number of births are related to each other and there may be some differences according to reproductive performance among cows. In this study, the relationship between artificial insemination time and some milk yield characteristics was investigated. There are many studies investigating the relationship between artificial insemination time and some reproductive performance traits. However, the number of studies investigating the relationship between artificial insemination time and some milk yield traits is rare.

Lactation Length

In this study, the average lactation length of Holstein cows was determined to be 372,3 days. This value is seen to be about 67,3 days longer than the 305 days of which is considered as the standard lactation length. In this study, results obtained in the lactation length, compared to literature results conducted on the Holstein breed: This value is lower than that reported by Mellado et al (2011), but it is longer than Afifi, Khalil & Salem (1992), Akman et al (2001), Duru & Tuncel (2002), Atil & Khattab (2005), Bilgiç & Alıç (2005), Sehar & Özbeyaz (2005), Erdem, Atasever & Kul (2007), Javed, Babar & Abdullah (2007), Özkök & Uğur (2007), Akkas & Sahin (2008), Cilek (2009), Bayrıl & Yılmaz (2010), Şahin & Ulutaş (2010), Koç (2012), M'hamdi et al (2012), Özyürek & Tüzemen (2015) and Alkoyak (2016). The effect of calving year on lactation length were statistically significant ($p<0,001$). This study is like the reports of Erdem, Atasever & Kul (2007), Cilek (2009), Bayrıl & Yılmaz (2010) and Şahin & Ulutaş (2010).

Lactation Milk Yield

In this study, the mean lactation milk yield of Holstein cows was 9042,4 kg. This value is higher than findings of Afifi, Khalil & Salem (1992), Akman et al (2001), Duru & Tuncel (2002), Bilgiç & Alıç (2005), Erdem, Atasever & Kul (2007), Özkök & Uğur (2007), Bayrıl & Yılmaz (2010), Şahin & Ulutaş (2010), Koç (2012), Özyürek & Tüzemen (2015) and Alkoyak (2016); but is than lower findings of Mellado et al (2011).

The effects of the calving year on lactation milk yields were shown to be substantial in this study and these findings are parallel with findings of Duru & Tuncel (2002), Bilgiç & Alıç (2005), Erdem, Atasever & Kul (2007), Özkök & Uğur (2007), Bayrıl & Yılmaz (2010), Şahin & Ulutaş (2010) and Koç (2012) but is not like finding of Alkoyak (2016).

305 Days Milk Yield

This research 305-days milk yields of Holstein cows are 4639,79 kg. This value is higher than values in other studies Afifi, Khalil & Salem (1992), Akman et al (2001), Duru & Tuncel (2002), Atil & Khattab (2005), Bilgiç & Alıç (2005), Erdem, Atasever & Kul (2007), Özkök & Uğur (2007), Akkas & Sahin (2008), Cilek (2009), Bayrıl & Yılmaz (2010), Şahin & Ulutaş

(2010), Koç (2012), M'hamdi et al (2012), Alkoyak (2016) but is lower than Mellado et al (2011).

The effect of calving years on 305 days milk yield was significant. Similar results were shown by some studies on Holstein cattle Duru & Tuncel (2002), Bilgiç & Alıç (2005), Erdem, Atasever & Kul (2007), Özkök & Uğur (2007), Cilek (2009), Bayrıl & Yılmaz (2010), Şahin & Ulutaş (2010).

ME-305 days milk yield (kg)

In this study, the mean mature equivalent (ME)-305 days milk yield of cows was 9051,8 kg. This value is parallel finding of Farin et al (1994), is higher than value of Bayrıl & Yılmaz (2010) however is lower than value of ElBoshra, Ali & Hassabo (2016). Effect of calving year, lactation number and artificial insemination time on ME-305 days milk yield was shown as significant. However, effect of calving season and calving age on ME-305 days milk yield was non-significant. Effect of calving season, calving year, lactation number and calving age on ME-305 days milk yield were found to be significant at the different levels in Bayrıl & Yılmaz (2010) research. This study was partially paralleled study of Bayrıl & Yılmaz (2010).

Dry period (day)

The dry period of Holstein cows was 54,0 days. The dry period of Holstein cows was between 61 and 98,15 days in previous studies. Value of this study was lower than findings of previous studies Afifi, Khalil & Salem (1992), Akman et al (2001), Sehar & Özbeyaz (2005), Erdem, Atasever & Kul (2007), Akkas & Sahin (2008), Cilek (2009), Bayrıl & Yılmaz (2010), Şahin & Ulutaş (2010), M'hamdi et al (2012), Alkoyak (2016). Effect of calving season, calving year, lactation number and calving age on dry period were found to be non-significant. However, the effect of calving year and lactation number on dry period was reported as significant by Bayrıl & Yılmaz (2010). The Effect of calving age on dry period was reported as significant by Erdem, Atasever & Kul (2007). Effect of calving season, calving year and lactation number on dry period was reported as significant by Akkas & Sahin (2008). The Effect of lactation number on dry period was reported as significant Alkoyak (2016).

Conclusion

In this study, milk yield in cows in farm was increased periodically from the first lactation to the fourth lactation, and the highest milk yield was obtained in 4th lactation. There was a statistically significant difference in ME-305 days milk yield between 1st lactation and 2nd, 3rd and 4th lactation milk yields ($P<0.05$).

There have been many reasons for cows affecting milk yield. As experience in dairy cattle increases, it is inevitable that both milk yield and fertility will increase. As the year progresses in the study carried out, the increase in milk yield increases year by year. A significant difference ($P <0.05$) was found between 2010 and the milk yield to be obtained between 2011, 2012 and 2013. It was also found that lactation, which is increasing as lactation number, is a drop-in milk yield. There was also a statistical difference ($P> 0.05$) between the milk yields of cows in terms of the season in which they gave birth, but not statistically. A statistical significance level ($P> 0.05$) was not determined when cows had a relationship between the calving age and milk yield.

In this study, the milk yield was low when insemination was made in the 0-12-hour period in the animals that 1-2 years old-calving. Also, insemination between 13-24 hours was positively related to high milk yield.

As a result, it was determined that milk yield performance increased from lactation 1st to lactation 4th in this study, and the best results in terms of milk yield and fertility were obtained from lactating cows. For this reason, it can be said that in Holstein race cultivation, which requires good care and nourishment, cows can be easily handled during at least 4 lactations provided that environmental and management-related conditions are also noted. In addition, the number of lactations increases by at least 4th milk yields up to lactation. This might be due to improvements in breeding, nutrition, and management practices (e.g., milk production selection and herd culling). Although lactation length was determined to be about optimum, the dry period was predicted to be less than optimal. By lengthening the dry time, it may be feasible to make more profitable animals. It may be concluded that Holstein cattle are effectively produced for milk output on the Osmaniye commercial farm under Türkiye circumstances and in the South Eastern Anatolia environment.

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Abdominal Tuberculosis In Children

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Introduction

Tuberculosis (TB) is one of the leading causes of death due to infection worldwide. According to the World Health Organization (WHO) Global Tuberculosis Report, the incidence of TB was 142/100.000 (Lukosiute-Urboniene & et al., 2021). In parallel with the increase in the number of human immunodeficiency virus (HIV) infection and multidrug-resistant tuberculosis cases, it has been reported that there has been an increase in the frequency of TB all over the world in the last 10 years (Kiliç & et al., 2015). In the pediatric age group, it is predicted that the annual number of new cases is approximately 1 million and the number of cases resulting in death is 450.000 (Dinler & et al., 2008, Lal & et al, 2020).

Extrapulmonary involvement is encountered in one third of all TB cases (Mehmood & et al., 2019). Although superficial lymph node involvement is most common in extrapulmonary TB, the central nervous system, gastrointestinal system, genitourinary system, and musculoskeletal system can also be involved. Parallel to the increase in other forms of TB, an increase is also observed in abdominal TB in recent years (Wong & et al.,2020).

Abdominal TB is a rare type of extrapulmonary TB, with a prevalence of between 0.3 to 4.3% among the childhood TB cases (Kiliç & et al., 2015, Dinler & et al., 2008). Abdominal TB usually develops a result of lymphohematogenous spread of the primary infection or adjacent to an abdominal focus or mesenteric lymph node. Although this disease may involve the gastrointestinal tract, peritoneum, mesenteric lymph nodes and solid organs, it is most commonly encountered as peritoneal involvement, and mostly affects young adults. In the children, abdominal TB is frequently observed in patients who are immunosuppressed or on continuous ambulatory peritoneal dialysis (Mehmood & et al., 2019). Among abdominal TB cases, mesenteric nodal disease often accompanies with other abdominal organ involvement. Isolated mesenteric tuberculosis lymphadenitis (IMTL) is a very rare manifestation of abdominal TB infection.

Clinical Findings

Although clinical findings in abdominal TB differ according to the site of involvement, fever, weight loss, abdominal pain, diarrhea, ascites, intestinal obstruction, perforation, and palpable mass are the leading causes of admission (Wong & et al., 2020). Some patients do not have signs of pulmonary TB. In these patients, although the PPD test is positive, there is no cough and night sweats and no TB findings on radiological imaging.

Differantial Diagnosis

In the differential diagnosis of abdominal TB; inflammatory bowel diseases, malignancies and other infectious diseases (Jadvar & et al., 1997). In cases, It may include non-

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pathognomonic radiological findings such as intraabdominal mass, mesenteric lymphadenopathy (LAP), ascites, hepatomegaly, splenomegaly, contamination in mesenteric fatty planes. In cases with abdominal tuberculosis, which can mimic malignancy with both clinical and radiological findings, it has been reported to be associated with increased CA125 while other tumor markers are negative (Çakır & et al., 2005).

Diagnosis

X-ray, abdominal ultrasonography (US) and CT are helpful radiological methods for the diagnosis in patients with abdominal TB (Figure 1). On US, lymph nodes can be seen individually or as clusters. In the center of lymphadenopathies, hypoechoic areas and calcifications are observed in some patients.

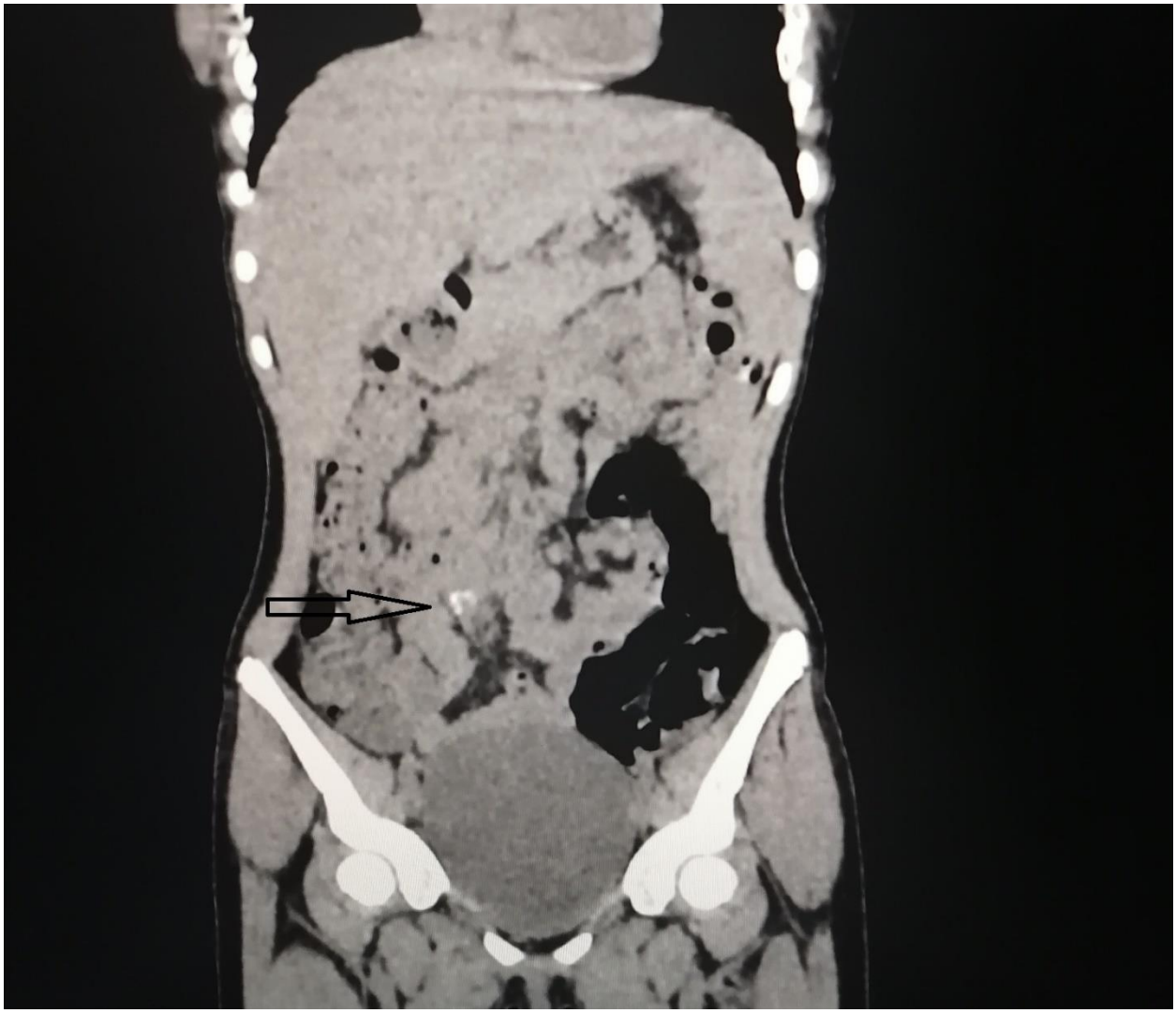

Figure 2. *Mesenteric calcified mass on coronal abdominal CT section.*

Diagnosis of abdominal tuberculosis is made by isolation of the agent by microbiological methods (direct examination for *Acid-resistant* bacteria *(ARB)* and/or Löwenstein Jensen medium culture, Bactec culture, polymerase chain reaction) from biopsy materials taken outside of laparotomy and/or laparotomy, and detection of granulomatous inflammation and caseification necrosis in histopathological examinations (Figure 2).

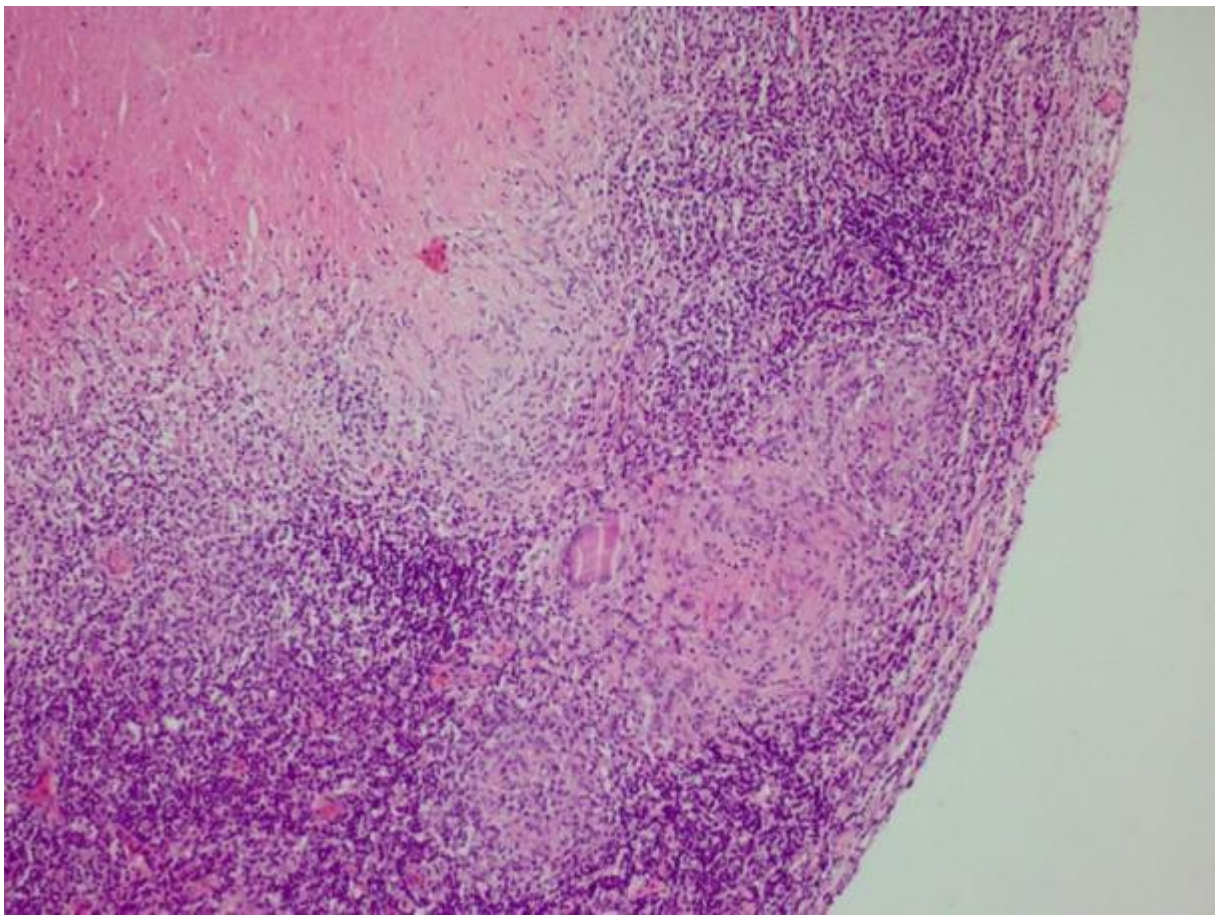

Figure 4. *Epitheloid histiocytes at the periphery with central caseation and Langhans giant cell, H&E, 10x*

Colonoscopic data of patients with abdominal tuberculosis show ulcers, nodules, deformed cecum and ileocecal valves, strictures, multiple fibrous bands, and polypoid lesions (Bayramiçli, Dabak G & Dabak R,al., 2003). Colonoscopic localizations and similarity of lesions may lead to diagnostic confusion between Crohn's Disease and intestinal tuberculosis. Peritoneal tuberculosis is a more common group among abdominal tuberculosis. In the diagnosis of peritoneal tuberculosis, ARB and culture studies in ascites that are aspirated more than one liter increase the sensitivity rate above 80%. (Akgün, Yılmaz & Taçyıldız, 2002). IMTL is rare in abdominal TB, and occurs as a result of the involvement of lymph nodes in the mesentary, ileocaecal and pyloroduodenal areas. Intestinal involvement may not be present in the patients. Abdominal mass may be palpable on the physical examination, and can cause intestinal or urinary obstruction by external pressure. Isolated lymph node involvement is more common in immunosuppressed patients and infections caused by drug-resistant bacteria (Mehmood & et al, 2019). IMTL can mimic mesenteric lymphadenitis, inflammatory bowel diseases, HIV, metastasis or lymphoproliferative diseases. Therefore, pathological examination of the lymph node and isolation of the agent by PCR are mandatory to achieve the correct diagnosis.

Treatment

As antituberculous treatment, isoniazid, rifampicin, ethambutol and pyrazinamide are used for the first two months. In addition, the combination of isoniazid and rifampicin is given to the patients for the next four months (Lal & et al, 2020). If necessary, treatment can be extended for up to two years. Surgical approach; It is limited to obstruction, perforation, fistula and

strictures. Some recent publications have reported that strictures and fistulas can respond to medical treatment (Bayramiçli, Dabak & Dabak, 2003).

Conlusions

The most important step in the diagnosis of abdominal tuberculosis is the clinician's suspicion of abdominal tuberculosis when nonspecific symptoms and signs are encountered. In case of doubt, early diagnosis, cost, mortality and morbidity will decrease with the diagnosis algorithm to be followed from non-invasive methods to more invasive methods.

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Carbon Monoxıde Poısonıng

Erdinç ŞENGÜLDÜR[1]

Carbon monoxide (CO) is a colorless, odorless gas. It is released as a result of incomplete combustion of carbon-based fuels. It is normally present in the air at less than 10 parts per million. It is also found in industrial substances in liquid or gas form (Rose et al., 2017). It is produced in trace amounts as a result of metabolism in the body. CO is usually taken into the body by inhalation. The affinity of CO for hemoglobin is about 240 times greater than that of oxygen. When CO binds to hemoglobin, it makes it difficult for hemoglobin to release oxygen to the tissues, which causes hypoxia and severe damage in tissues with high oxygen demand (Eichhorn, Thudium, & Jüttner, 2018).

Every year, between 20,000 and 50,000 cases of CO poisoning are reported in the United States. Again, according to the USA data, it is seen that the average mortality is between 1% and 3%. The mortality rate in cases of poisoning due to suicidal inhalation of gases is higher than in cases of accidental exposure. Between 1000 and 1200 deaths from CO poisoning are reported annually in the USA. Seasonal and regional variations are observed in accidental exposure cases. An increase is observed in countries with cold climates, especially in winter (Megas, Beier, & Grieb, 2021). Improperly manufactured heating systems are the most common cause. It has been reported that generators activated due to power cuts occasionally cause CO poisoning. Incorrect positioning of generators or improper chimney systems cause poisoning. Cases of CO poisoning due to hookah, the use of which has increased recently, have been reported in our country. The risk is high in cafes and restaurants that serve hookah indoors. Methylene chloride is a substance used in industry as a solvent and paint remover. When inhaled or taken orally, CO is formed as a result of metabolism in the liver. Its use is banned worldwide because it causes CO poisoning, but it can still be found in many dyestuffs (Guzman, 2012).

Pathophysiology:

Impaired Oxygen Delivery: CO binds with great affinity to the iron portion of hemin and other protoporphyrins. Hemoglobin is a tetramer molecule. It has four oxygen-binding sites. The affinity of CO for hemoglobin is 240 times that of oxygen. When CO binds to hemoglobin, it forms carboxyhemoglobin (COHB). The binding of CO both reduces the oxygen-carrying capacity and causes an allosteric change that makes it difficult for hemoglobin to release oxygen to the tissues. The oxyhemoglobin dissociation curve shifts to the left. Damage develops in cells that need high amounts of oxygen, such as neurons (Chenoweth, Albertson, & Greer, 2021).

Impairment of Oxygenated Respiration: CO binds to molecules such as myoglobin, cytochromes, and NADPH Reductase, resulting in disruption of mitochondrial oxidative phosphorylation. lactic acidosis develops. When it binds to myoglobin, it impairs cardiac

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contractility. Even if adequate oxygenation is provided in CO intoxications, myocardial involvement may continue (Goldstein M. 2008).

Formation of Reactive Oxygen Derivatives: CO causes superoxide formation and oxidative stress, possibly resulting in lipid peroxidation and neurological damage (Chenoweth J.A., Albertson T.E. & Greer M.R. 2021).

Activation of Inflammatory Process: CO activates platelets and causes nitric oxide (NO) to be released from their superficial hemoproteins. Free NO reacts with superoxides to form peroxynitrite. Peroxynitrite inhibits mitochondrial functions and increases platelet activation. Activated platelets stimulate neutrophils and cause myeloperoxidase (MPO) release. MPO further increases the inflammatory process, more neutrophils are activated. As a result, endothelial damage develops (Goldstein, 2008).

Symptoms:

Patients may present to the emergency department with many non-specific findings. Mild and moderate patients present with symptoms such as malaise, malaise, and headache. People whom CO mildly poisons are similar to upper respiratory tract infection patients. Loss of consciousness is an important finding. It should be carefully questioned whether there is loss of consciousness, it is important in terms of the need for hyperbaric oxygen therapy.

Headache, nausea, dizziness, drowsiness, vomiting, confusion, shortness of breath, syncope, chest pain and weakness are the symptoms that can be seen (Raub, Mathieu-Nolf, Hampson, & Thom, 2000).

Examination:

Examination findings of CO poisoning are limited to mental status changes, tachycardia, and tachypnea, unless there are traces of trauma or burns. Patients may present with symptoms ranging from mild confusion to deep coma. The appearance of a cherry red spot on the lips is not a specific or sensitive finding (Durmaz, Laurence, Roden, & Carruthers, 1999).Patients with any of the following findings should be considered severe CO intoxication:

Neurological: seizure, syncope, transient unconsciousness, coma

Metabolic: lactic acidosis

Cardiac: Ventricular arrhythmias, myocardial injury, pulmonary edema

Myocardial injury is common in moderate to severe CO poisoning and is associated with increased mortality. A retrospective study conducted with 230 patients showed that one-third of the patients with moderate and severe CO intoxication had myocardial damage (Choi, 2001).

Delayed Neuropsychiatric Syndrome (DNS) usually occurs within the first 20 days after CO exposure, but can occur up to 240 days. Neurological deficits may persist for 1 year or more. Personality changes, cognitive disorders, movement disorders, focal neurological deficits may develop. It is seen in 15%-40% of patients with severe CO intoxication (Varon, Marik, Fromm, & Gueler, 1999).

LNS development is not directly related to CO levels. Although it has not been fully elucidated, ischemia-reperfusion injury that develops when CO levels decrease and oxidative stress are responsible for the development of LNS (Varon et al., 1999).

Diagnosis:

Anamnesis is very important in diagnosis. The injured people who were rescued from the fire, families who stated that they lived in a house with a stove and applied with flu-like complaints, people who smoked indoor hookah or were exposed to its smoke, workers who might be exposed to exhaust gases during their work should be investigated for CO intoxication. Diagnosis is made by the high level of COHb in blood gas samples taken. For non-smokers, this value should be below 3%. The COHb value may increase up to 10% in smokers (Jüttner et al., 2021).

The high COHb level confirms the exposure of the patients, but may not correlate with the severity of the case. While COHb levels may be relatively low in patients presenting in the later stages of exposure, neurological and cardiac symptoms may be severe. The treatment should be guided by the patient's symptoms and signs, not the COHb level (Jüttner et al., 2021).

ECG should be requested in all symptomatic patients. Signs of ischemia or infarction may be seen. Cardiac enzymes should be requested in people with ECG findings and in people with a history of cardiac disease.

Blood gas analysis, CBC, blood biochemistry, pregnancy test, chest X-ray should be requested. COHb measurement by spectrophotometry is the standard method to confirm the diagnosis of CO exposure.

MRI and CT findings are not seen in the early stages of intoxication, and hemorrhages in the deep white matter and globus pallidus can be seen in the later stages (Jüttner et al., 2021).

Management-Treatment:

The first intervention to be done is to end the exposure of people and to start giving high-flow oxygen as soon as possible (Ruth-Sahd, Zulkosky, & Fetter, 2011).

It should be considered that the people around the patients brought due to involuntary exposure may also be poisoned. Persons in charge should be informed and other possible patients should be checked.

High-flow oxygen therapy: Initial treatment in patients with suspected or confirmed CO poisoning is high-flow (100%) oxygen with a reservoir mask. CO elimination begins when the patient is removed from exposure, but the COHb half-life is between 250-300 minutes in room air. When 100% oxygen is given with a reservoir mask, this time decreases to 75-90 minutes (Hampson, Piantadosi, Thom, & Weaver, 2012). Normobaric high-flow oxygen therapy is an inexpensive and easily applicable treatment. Studies have shown that oxygen therapy significantly reduces the development of DNS (Wang et al., 2022).

Serious poisonings: ABC (airway, breathing, circulation) is evaluated primarily in critically ill patients. In the patient with no pulse, cardiopulmonary resuscitation (CPR) is started immediately. Patients with severe mental status impairment, coma or respiratory distress should be intubated and ventilated with 100% oxygen (Roderique, Josef, Feldman, & Spiess, 2015).

Hydroxycobalamin treatment: It should be kept in mind that cyanide poisoning may also be present in unconscious patients rescued from fire and exposed to smoke, in poor general condition. Choosing the correct diagnosis between cyanide and CO poisoning is difficult because they develop for similar reasons and cause similar clinics. Empirical hydroxycobalamin therapy is recommended for patients exposed to fire smoke. Hydroxycobalamin treatment is given as 70 mg/kg iv, it can be repeated after 15 minutes if the clinic does not improve. The standard adult dose is 5 g IV. Hydroxycobalamin treatment will cause the COHb result in the blood to be inaccurate. Blood gas should be taken before treatment

if possible. If blood gas has not been taken before, the clinician should be informed that hydroxycobalamin was given (Roderique et al., 2015).

Hyperbaric Oxygen therapy: Which patients should be given?

• Patients with COHb >25%

• Patients with COHb> 15% who are pregnant

• Patients with unconsciousness

• Patients who develop severe metabolic acidosis

• Patients with end-organ damage (focal neurological deficits, ECG abnormalities, cardiac enzyme elevations)

Patients are ventilated with 100% oxygen at pressures above normal atmospheric pressure. The COHb half-life is reduced from 75-90 minutes to 30 minutes. The earlier hyperbaric oxygen therapy is started, the more effective it will be. It is ideal to start in the first 6 hours (Guzman, 2012). Tissue oxygenation will increase as carboxyhemoglobin is eliminated. Hyperbaric oxygen therapy also increases the amount of dissolved oxygen in the blood, thus positively affecting tissue oxygenation. It was observed that lipid peroxidation and xanthine oxidase formation, which cause the development of DNS, decreased with hyperbaric oxygen therapy. Studies have shown that hyperbaric oxygen therapy reduces the development of DNS and mortality (Reumuth et al., 2019).

Although rare, complications may develop due to hyperbaric oxygen therapy: Pneumothorax, Ear barotrauma, Seizure due to oxygen toxicity (usually after multiple and long treatments), Gas embolism.

The only and absolute contraindication for hyperbaric oxygen therapy is untreated pneumothorax (Sen & Sen, 2021).

Discharge:

Reservoir mask and 100% oxygen therapy will usually be sufficient for patients who do not have serious clinical findings and do not need hyperbaric oxygen therapy. Patients' symptoms will quickly regress. Repeated blood gas measurements are not necessary for monitoring therapy.

Hospitalization should be considered for patients whose symptoms do not regress, and patients whose ECG and laboratory parameters indicate severe poisoning. It would be beneficial to evaluate patients with suspected suicide by the psychiatry department before hospitalization (Weaver, Valentine, & Hopkins, 2007).

Special Groups:

Children: In the infant age group, the symptoms may be more subtle and difficult to notice. Infants and young children present with nonspecific symptoms such as feeding difficulties and fussiness. However, symptoms will appear more quickly in younger children than in older children. The fact that older children can talk and tell about symptoms such as nausea and headache will provide convenience in terms of diagnosis. DNS development is less common in the pediatric age group (Chang et al., 2017).

Diagnosis and treatment approach are not different in carbon monoxide poisonings of pediatric patients. Hyperbaric oxygen therapy centers do not make any changes in their approach, however;

• Myringotomy should be performed before hyperbaric therapy in children under 5 years of age with active otitis media or in children who cannot balance the middle ear pressure (Liebelt, 1999).

• A family member may be allowed to accompany the children as they are afraid to enter the hyperbaric chamber alone.

• It should be kept in mind that infants may develop hypothermia easily. Care should be taken in terms of hypothermia.

• Congenital defects should be taken into account, pneumothorax may develop in the presence of emphysema or open ducts may close due to pressure in congenital heart diseases.

Pregnant Patients: The indication for hyperbaric oxygen therapy in pregnant patients is different because CO has a higher affinity for fetal hemoglobin and a longer half-life when bound. Hyperbaric oxygen therapy is indicated in pregnant patients even at lower COHb values. Although there is no study showing that exposure to hyperbaric oxygen adversely affects the fetus, studies on this subject are also limited (Arslan, 2021).

Late Results:

Neurological and cognitive disorders are the most common cause of morbidity in the late period. Various levels of neurologic sequelae are seen in 40% of patients who recover from severe intoxication. Myocardial damage is the most common cause of long-term mortality. Studies have shown that the long-term mortality of patients with myocardial involvement is 2 times higher than those without (Henry et al., 2006).

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Analytical Approaches to the Fertility Loss in High-Yielding Dairy Cattle

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Introduction

In recent decades, there has been a notable trend toward increasing milk yield in the dairy industry because the efficiency of milk production plays a crucial role in the success of dairy farms. This progress has been achieved through advancements in genetics, nutrition, and management practices.

However, this emphasis on enhancing milk yield has also been accompanied by a decline in fertility rates among certain dairy breeds. This decline can be attributed to the singular focus on increasing milk production, which can adversely affect fertility. To address this concern, there is now a heightened focus on striking a balance between milk yield and fertility when selecting dairy cows.

It is important to recognize that there is significant variation in milk yield and fertility performance both across different dairy breeds and within individual cows. Consequently, while there may be an overall inclination towards boosting milk production, the performance of individual cows and herds can vary considerably based on factors such as genetics, nutrition, management practices, and environmental conditions.

When breeding cows, farmers must carefully consider the trade-off between milk production and reproductive capacity. If there exists a negative genetic correlation between milk yield and fertility, farmers may need to prioritize fertility to ensure long-term reproductive success. On the other hand, if there is a positive genetic correlation between milk yield and fertility, farmers may be able to simultaneously select for both traits.

Adopting a comprehensive and integrated approach that encompasses genetic selection, nutrition, health management, reproductive management, and environmental stewardship can greatly contribute to improving milk yield and fertility rates in a dairy herd. This holistic approach is vital for ensuring sustainable and profitable dairy production.

Overview

The optimum milk yield for a dairy cow is the level of milk production that maximizes profitability while maintaining animal health and welfare depends on several factors, including breed, management practices, and environmental conditions (Chetroiu et al, 2022).

The decrease in reproductive ability in high-yielding dairy cows is believed to be caused by a combination of factors, including nutritional imbalances, metabolic stress, and altered hormone levels (Walsh et al., 2011). Some of the mechanisms that may contribute to this decrease in reproductive ability are:

Negative energy balance: High-yielding dairy cows often experience a negative energy balance, which means that their energy intake is insufficient to meet their energy requirements

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for milk production. This can result in reduced body condition, altered hormone levels, and impaired reproductive function (Stancliffe et al., 2011).

Metabolic stress: The high metabolic demands of milk production can also cause metabolic stress, which can affect the immune system, reproductive performance, and product quality as well as animal welfare. This can impair ovarian function and reduce fertility (Gross and Bruckmaier, 2019).

Disruption of hormone levels: High milk yield can also disrupt the balance of the reproductive system, such as poor expression of estrus, defective oocytes/embryos and uterine infections which are critical for ovarian function and fertility (Dobson et al., 2007).

Nutritional imbalances: High-yielding dairy cows may also experience imbalances in essential nutrients, such as protein, minerals, and vitamins, which can impact reproductive function (Bindari et al., 2013).

Genetic selection: In some cases, the genetic selection for high milk yield may also indirectly affect reproductive ability by selecting cows with a higher risk of reproductive disorders or metabolic stress (Oltenacu and Broom, 2010).

These factors can interact and contribute to a complex cascade of events that lead to reduced reproductive ability in high-yielding dairy cows.

Significance of milk yield and fertility in the dairy sector

Milk yield is a critical factor in the efficiency, profitability and sustainability of the dairy industry and has played an important role in the development and evolution of dairy farming over time. It is influenced by a variety of factors, including genetics, nutrition, management practices, and environmental factors. For example, cows that are well-fed and well-cared for are more likely to have higher milk yields than cows that are underfed or poorly managed (Cwalina et al., 2020).

Since milk yield is directly linked to the revenue generated by a dairy farm. Farmers are paid for the milk that their cows produce, so higher milk yield means higher revenue and profitability (Schorr and Lips, 2018) which can improve the efficiency of a dairy operation. Maximizing milk yield through selective breeding and intensification of production systems has been the key driver of genetic improvement in dairy cows, which has led to the development of high-yielding dairy breeds, improving the understanding of a sustainable management system (Brito et al., 2021).

Milk and dairy products are also important parts of many people's diets, and the dairy industry plays a vital role in meeting this demand. Milk yield is an important factor in ensuring a reliable supply of milk and dairy products for consumers (Pieper et al., 2016).

Fertility refers to the ability of a cow to conceive and carry a calf to term in dairy systems. It is a critical aspect of dairy cow performance, as it directly impacts the reproductive success and profitability of a dairy herd. Fertility is also an important aspect of animal welfare in the dairy sector, as cows that are unable to conceive or carry a calf to term may experience health problems or be at risk of culling (Al Sidawi et al., 2021).

Fertility is a critical factor in the dairy sector for several reasons:

Reproductive success: Fertility is essential for the reproductive success of a dairy herd. If cows are not able to conceive and carry a calf to term, the size of the herd will decrease over time (Westwood et al., 2002).

Profitability: Fertility is directly linked to the profitability of a dairy operation. If cows have low fertility rates, farmers may need to invest in additional breeding programs or technologies, which can be costly.

Efficiency: Cows that have good fertility rates are more efficient at producing milk over their lifetimes, as they can produce more calves and enter the milking herd more quickly (Consentini et al., 2021).

Genetic improvement: Selective breeding for improved fertility has been a key driver of genetic improvement in dairy cows, leading to the development of high-fertility dairy breeds (Lucy, 2019).

Importance of Cow Milk for Human Consumption

The importance of cow milk for human consumption is multifaceted and linked to various social, economic, and cultural impacts associated with livestock keeping and production. Dairy farming, in particular, is considered a vital tool for reducing poverty in lower-income areas. Not only can dairy cattle provide a source of milk and meat, but keeping healthy livestock can also help to reduce the burden of disease and improve household nutritional status, which can lead to increased household income, wealth, access to education, and access to health care (Grout et al., 2020).

Cow milk has a rich heritage in human dietary practices and remains a highly popular beverage globally. Cow milk accounts for a significant 83% of total milk production worldwide (Bittante et al., 2022). This wholesome dairy product is a source of essential macronutrients, minerals, vitamins, and bioactive compounds, the levels of which are influenced by various factors including genetics, health, lactation stage, and animal nutrition (Cimmino et al., 2023).

Optimal Milk Yield by Genotype

The optimal milk yield for dairy cows can vary depending on the breed, as different breeds have different genetic potential for milk production. If a few examples of popular breeds over the Holstein, Guernsey and Swiss Brown breeds are given, it may be useful to express the following information:

Holsteins are the most common dairy breed in the world and are known for their high milk production. Holsteins have an average milk production between 5000-10000 kg per lactation while Jerseys are a smaller breed of dairy cow that is known for producing high-quality milk with a high butterfat content. Jerseys have an average milk production between 4000- 8000 kg per lactation (Alqaisi et al., 2020; Coffey et al., 2016; Kristensen et al., 2015; Mogollón-García et al., 2020).

Guernseys are a medium-sized dairy breed that is known for producing rich, creamy milk with a high butterfat content. Guernseys have an average milk production of around 6000 kg per year (Cruickshank et al, 2002).

Brown Swiss: Brown Swiss cows are a larger breed of dairy cow that are known for their hardiness and adaptability. Brown Swiss cows have an average milk production of around 6000-7000 kg per year (Mylostyvyia et al., 2021).

It is important to note that these are general averages and individual cows can produce more or less milk depending on a range of factors such as genetics, nutrition, management practices, and environmental conditions.

Genetic Correlations Between Milk Yield and Fertility in Dairy Cows

The success of a dairy farm depends on the ability of cows to produce milk efficiently, as well as their reproductive capacity. Milk yield and fertility are two essential traits in dairy cows and genetic correlations between these traits can have a significant impact on dairy farming in terms of success and sustainability.

Genetic correlations between milk yield and fertility in dairy cows are complex and depend on various factors. The relationship between milk yield and fertility has significant implications for dairy farming, and farmers must carefully consider this relationship when breeding cows to ensure long-term success.

Some studies have reported a negative genetic correlation between milk yield and fertility (Lehmann et al., 2016; Pryce et al., 1998; Rauw et al., 1998; Walsh et al., 2011). This negative correlation suggests that cows that produce more milk tend to have lower fertility rates. One reason for this negative correlation is that cows that produce more milk require more energy to maintain milk production, which can reduce their reproductive capacity. Additionally, some cows may divert resources away from reproduction to prioritize milk production.

On the other hand, some studies have reported a positive (Beneberu et al., 2021) or zero genetic correlation (Raheja et al. 1989) between milk yield and fertility. The positive correlation suggests that cows that produce more milk tend to have better fertility rates. One reason for this positive correlation is that cows that produce more milk may have a higher genetic potential for overall productivity, including reproduction.

The condition may vary during different periods of lactation. The initial weeks of lactation play a critical role, particularly in highly productive dairy cows. During this period, a significant energy deficiency arises as a result of a substantial increase in milk production while facing physiological limitations on energy intake. Consequently, the cow must tap into its adipose stores and, in some cases, even its muscle tissue to acquire the necessary energy, resulting in weight loss. The post-calving nutritional status of the cow has implications for disease resistance and reproductive performance, with energy-related factors overlapping with fertility traits. It has been observed that, in certain populations, there exists an unfavorable correlation between fertility traits and milk production. This is attributed to the competition for limited bodily resources between these traits (Strucken et al., 2012).

Farmers must balance milk production and reproductive capacity when breeding cows. If there is a negative genetic correlation between milk yield and fertility, farmers may need to prioritize fertility when breeding cows to ensure long-term reproductive success. If there is a positive genetic correlation between milk yield and fertility, farmers may be able to select for both traits simultaneously.

Cow Milk Production by Country and Region

The optimum milk yield in dairy cows can vary depending on the regions and countries due to differences in management practices, environmental conditions, and genetics.

The production of milk in industrialized regions such as the European Union (EU), the United States of America (US), New Zealand and Australia is higher than their domestic demand. This surplus of production encourages these regions to export milk to countries that do not produce enough. The dairy sector differs among countries in terms of production models, animal species, breeds, connections to production zones, actors, public policies, and human diets (SraÏri et al., 2019).

In the United States, the optimum milk yield for high-producing Holstein cows, which are the most common dairy breed, is typically around 40-50 kg per day in early lactation. However, milk yields can vary widely depending on the management system, with some farms aiming for higher yields and others aiming for lower yields (VandeHaar and St-Pierre, 2006).

In Europe and Russia, the optimum milk yield can vary depending on the region and management practices. For example, in the Netherlands, Denmark and Russia milk yields of 10,000-12,000 kg per year per cow can be seen where intensive technologies are used in modern dairy complexes (Kristensen et al., 2015; Lyashenko et al., 2022). In contrast, in grazing-based systems, such as those in Ireland and the United Kingdom, milk yields are often lower, with a focus on maintaining animal health and fertility (Craig et al., 2022; Marumo et al., 2022).

In New Zealand, the optimum milk yield for dairy cows is generally lower than in other countries, with a focus on maximizing pasture utilization and reducing reliance on supplementary feeds. Milk yields of 3000-4000 kg per year per cow are common, although some farmers may aim for higher yields (Edwards et al., 2014; Edwards, 2019).

In developing countries, the optimum milk yield can vary widely depending on the local context. In some cases, small-scale farmers may aim for low milk yields to maintain animal health and reduce feed costs, while in other cases, larger commercial farms may aim for higher yields to maximize profitability.

At this point, it can be said that optimum milk yield in dairy cows depends on a range of factors, including genetics, management practices, and environmental conditions, and will vary widely between regions and countries.

Research Efforts to Improve Milk Yield in Dairy Cows

In recent years, genomic research is being used to identify genes that are associated with high milk yield and to develop breeding strategies that can increase milk production. By sequencing the DNA of dairy cows, researchers can identify genes that are linked to traits such as milk yield, fertility, and disease resistance. This information can be used to selectively breed cows that have a higher milk yield (Korku´c et al., 2023).

On the other hand, nutrition is a key factor in milk production, and researchers are studying the effects of different diets on milk yield. For example, researchers are investigating the use of feed additives such as probiotics and prebiotics to improve the digestion and absorption of nutrients in cows (Nalla et al., 2022). They are also studying the effects of different types of forages and grains on milk yield (Guo et al., 2022) as well as supplements on the reproductive performance of cows, with a focus on optimizing the timing and duration of ovulation.

Reproduction is another key factor in milk yield, and researchers are studying ways to improve the reproductive efficiency of dairy cows. This includes research into the use of artificial insemination and embryo transfer techniques, as well as studies of the hormonal and genetic factors that affect fertility. They are also studying the use of new technologies such as sexed semen, which allows for more precise control over the sex of offspring, and in vitro fertilization, which can increase the number of embryos produced per cow (Nowicki, 2021).

Above all, the health of dairy cows is critical to their ability to produce milk, and researchers are studying ways to prevent and treat diseases and other health problems that can affect milk production (Abegaz, 2022). This includes research into the use of vaccines, antibiotics, air quality, lighting and other treatments to prevent and treat diseases such as mastitis, lameness, and reproductive disorders.

The goal of these research efforts is to improve the efficiency and sustainability of dairy production, while also ensuring the welfare of dairy cows.

Obstacles To Achieving Significant Improvements

Although genomics research is helping to identify genes associated with high milk yield, genetic improvement can take time as it is a slow process. Breeding cows with desirable traits take several generations, and it can take years or even decades to develop a cow population with consistently high milk yields.

Environmental factors such as weather conditions, temperature, and housing can also affect milk yield. For example, heat stress can reduce milk yield in dairy cows, and poor ventilation can increase the risk of respiratory disease, which can also affect milk production (Liu et al., 2019).

The quality of feed and the availability of forage can also affect milk yield. If cows do not have access to high-quality feed or if their feed is contaminated with toxins or pollutants, their milk yield may decrease (Johansen et al., 2018).

Health issues such as mastitis, lameness, and reproductive disorders can also reduce milk yield. These issues can be caused by a range of factors, including poor nutrition, environmental conditions, and infectious agents (Logroño et al., 2021).

Implementing new technologies or making changes to management practices can be costly for dairy farmers, especially small-scale ones. Improving milk yield may require investments in new equipment or infrastructure, which may not be affordable for all farmers (Gaworski, 2021).

Some approaches to improving milk yields, such as the use of growth hormones or intensive confinement, raise ethical concerns among consumers and activists, which can limit the adoption of these practices.

Overall, improving milk yield requires a comprehensive approach that takes into account genetics, nutrition, environmental conditions, animal health, cost, and ethical concerns.

The Future Projection of Milk's Role in Human Life

It will depend on a range of factors, including changes in dietary preferences, advancements in technology, and concerns about animal welfare and the environment.

On one hand, cow milk has long been a staple food in many cultures and is a rich source of nutrients such as calcium, vitamin D, and protein. As the global population continues to grow and as people in developing countries become more affluent, there may be an increasing demand for dairy products, including cow milk (Lee et al., 2018).

On the other hand, there are concerns about animal welfare and the use of antibiotics and hormones in dairy production. As consumers become more conscious of these issues, they may seek out alternative sources of milk or dairy products from farms that use sustainable and ethical practices (Senthil Kumar et al., 2018)

In short, while cow milk will likely continue to play a significant role in human nutrition in the future, its importance may decrease or shift as dietary preferences, technology, and societal concerns evolve.

Strategies to Improve Milk Yield and Fertility Rates

Genetic selection: Selective breeding for high milk yield and fertility rates can help to improve the genetics of a dairy herd over time. Farmers should work with their breeding advisors to select bulls with high estimated breeding values (EBVs) for milk yield and fertility (Brito et al., 2021).

Nutrition: A balanced and well-managed nutrition program is essential for maintaining good milk yield and fertility rates. Farmers should work with a nutritionist to develop a feeding program that meets the specific needs of their herd (Mpairwe and Mutetikka, 2022).

Health management: Good health management practices, including vaccination programs, disease prevention strategies, and routine herd health checks, can help to maintain good fertility rates and milk yield (Sunum, 2020).

Reproductive management: Effective reproductive management strategies, including proper heat detection, timed breeding programs, and the use of artificial insemination (AI), can help to improve fertility rates in a dairy herd (Crowe et al., 2018).

Environmental management: A well-managed environment, including comfortable housing, clean water, and proper ventilation, can help to minimize stress on cows and maintain good fertility rates and milk yield (Pulinaa et al., 2020).

To summarize, a comprehensive and integrated approach that incorporates genetic selection, nutrition, health management, reproductive management, and environmental management can help to improve milk yield and fertility rates in a dairy herd and ensure sustainable and profitable dairy production.

Conclusion

The dairy industry is constantly evolving and adapting to changes in technology, consumer demand, and environmental concerns. Optimum milk yield will depend on a range of factors, including the goals of the farm, the available resources, and the genetics and management practices of the cows. Dairy farmers need to work with their veterinarians and other advisors to determine the best milk yield targets for their specific situation.

There are genetic factors that affect both milk yield and fertility in dairy cows. This means that breeding for high milk yield may also lead to reduced fertility, and vice versa. By selecting specific genetic traits, dairy farmers can aim to balance milk yield and fertility.

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Aı In Medıcıne

Omer SEVINC[1]

Introduction

Artificial Intelligence (AI) is revolutionizing many industries, including healthcare. AI in medicine refers to the application of AI technology and techniques to healthcare, with the goal of improving the quality of medical care and enhancing patient outcomes.

The use of AI in medicine is growing rapidly, and there are a range of applications for this technology in the healthcare industry, including diagnosis, treatment planning, and drug discovery. AI can be used to analyze large amounts of medical data, such as patient records and imaging studies, to identify patterns and make predictions about patient outcomes. This information can then be used to inform clinical decision-making, improve patient care, and optimize healthcare delivery.

AI in medicine has the potential to revolutionize healthcare, but it also raises important ethical and legal issues that must be carefully considered and addressed. These issues include data privacy and security, bias and discrimination, responsibility and accountability, and autonomy and decision-making.

Despite these challenges, the future of AI in medicine is promising. With advances in AI technology and growing demand for better, more efficient healthcare, it is likely that AI will continue to play an increasingly important role in the healthcare industry. The responsible and ethical development and implementation of AI in medicine will be crucial in realizing its full potential and delivering better outcomes It is important to note that AI in medicine is still in its early stages, and much work remains to be done to fully realize its potential. However, the progress that has been made so far is very promising, and there are many exciting developments on the horizon.

One of the key areas where AI is having a significant impact is in the diagnosis of medical conditions. AI algorithms can analyze large amounts of medical data, such as imaging studies and patient records, and use this information to identify patterns and make predictions about patient outcomes. This can help healthcare providers to diagnose conditions more accurately and quickly, and to develop more effective treatment plans.

Another area where AI is having a major impact is in drug discovery. AI can be used to analyze vast amounts of data related to disease biology, drug interactions, and patient outcomes, and to identify new drug targets and potential treatments. This can help to speed up the drug discovery process and to develop new treatments that are more effective and have fewer side effects.

Despite these benefits, the use of AI in medicine also raises important ethical and legal issues. For example, there is a risk that AI algorithms could perpetuate existing biases and discrimination in healthcare, and that sensitive patient data could be misused or exploited. It is

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therefore crucial that AI in medicine is developed and implemented in a responsible and ethical manner, and that the industry works closely with experts in ethics, law, and computer science to address these important issues.

In conclusion, the use of AI in medicine has the potential to revolutionize healthcare and deliver better outcomes for patients. However, to realize this potential, it will be important to continue to invest in research and development, and to address the ethical and legal issues that arise from the use of this technology. With the right approach, AI has the potential to transform the healthcare industry and to deliver better, more efficient care to patients around the world. for patients.

Definition Of AI In Medicine

AI in medicine refers to the application of artificial intelligence (AI) technologies to the field of healthcare, with the goal of improving patient outcomes, streamlining healthcare delivery, and enabling more personalized and efficient care. This can include the use of machine learning algorithms, natural language processing (NLP), computer vision, and other AI technologies to analyze patient data, support clinical decision-making, improve medical imaging, and develop new drugs and treatments, among other applications. The goal of AI in medicine is to leverage the power of AI technologies to provide more effective, efficient, and accessible healthcare to patients (Mintz, Y., & Brodie, R., 2019).

AI in medicine involves the use of advanced computational methods and machine learning algorithms to analyze large amounts of patient data, including medical records, imaging studies, laboratory results, and other clinical information. The goal is to use this data to support clinical decision-making, improve patient outcomes, and streamline healthcare delivery.

One of the key benefits of AI in medicine is its ability to process vast amounts of data, identify patterns and trends that might not be noticeable to the human eye, and provide insights that can inform treatment decisions and improve patient outcomes. For example, AI algorithms can be used to analyze medical images, such as CT scans or MRI studies, to detect signs of disease or injury that might not be apparent to a human radiologist (Pesapane, F., Codari, M., & Sardanelli, F., 2018).

Another key application of AI in medicine is the development of personalized medicine. AI algorithms can be used to analyze a patient's genetic information, medical history, lifestyle factors, and other data to provide personalized recommendations for treatment and care. This can lead to more effective and efficient healthcare delivery, as well as better patient outcomes.

AI is also being used to improve remote patient care, enabling healthcare providers to reach patients in remote or underserved areas. For example, AI algorithms can be used to provide remote monitoring of patients, alerting healthcare providers to changes in a patient's condition, and enabling them to intervene in a timely manner.

In addition to these applications, AI is being used to support clinical decision-making and to optimize the drug discovery process. AI algorithms can be used to assist healthcare providers in making more informed decisions about patient care, based on the analysis of large amounts of data, and to streamline the drug discovery process by helping to identify new targets for drug development and optimizing clinical trial design (Szolovits, P., 2019).

Overall, AI has the potential to transform the field of healthcare, providing more effective, efficient, and personalized care to patients and improving patient outcomes. However, it is important to ensure that AI technologies are developed and integrated into clinical practice in a safe, effective, and responsible manner (Coiera, E. W., 1996).

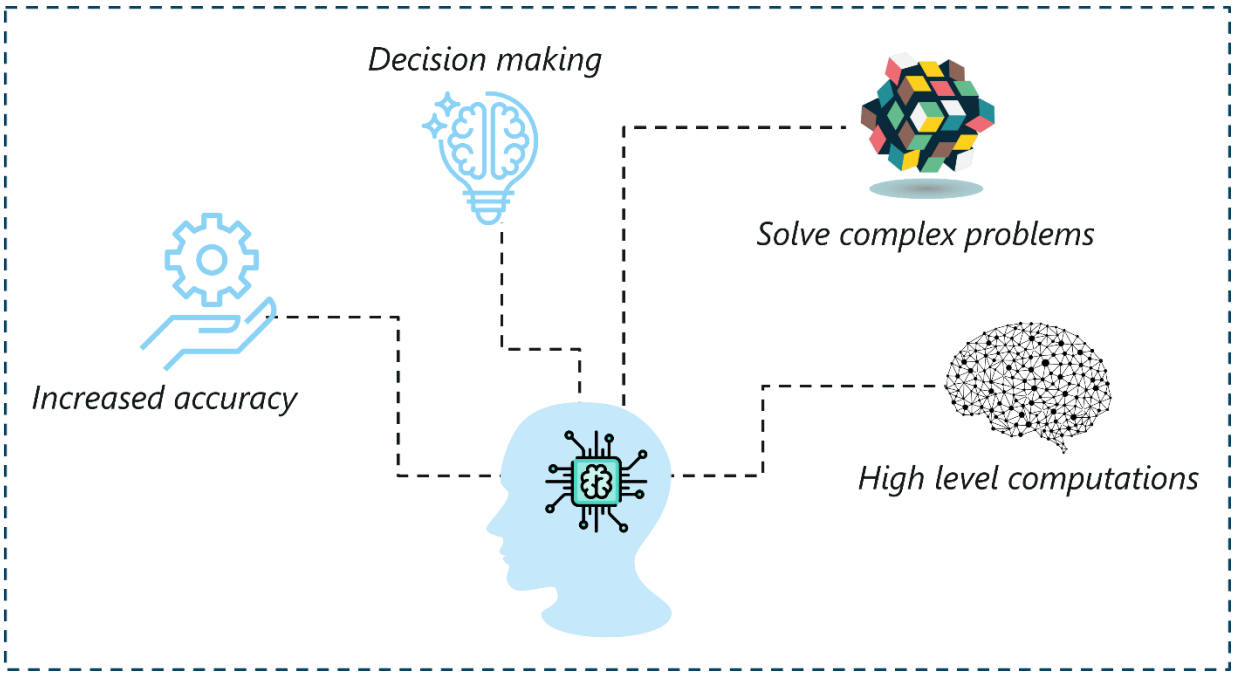

Figure-1 AI provides solutions by decision making in AI. (edureka, 2023)

Overview of AI in the Healthcare Industry

Artificial intelligence (AI) is becoming increasingly prominent in the healthcare industry, with the potential to revolutionize the way healthcare is delivered and improve patient outcomes. The use of AI in healthcare has been driven by the increasing availability of electronic health records, the growing need for more efficient and cost-effective healthcare delivery, and the desire to provide more personalized care to patients (Lee, D., & Yoon, S. N., 2021).

AI is being applied to a wide range of healthcare tasks, including the analysis of medical images, the development of personalized treatment plans, and the optimization of clinical decision-making. Some of the key applications of AI in healthcare include:

Medical imaging: AI algorithms can be used to analyze medical images, such as X-rays, CT scans, and MRI studies, to detect signs of disease or injury that might not be apparent to human radiologists.

Personalized medicine: AI algorithms can be used to analyze a patient's genetic information, medical history, and other data to provide personalized recommendations for treatment and care.

Remote patient monitoring: AI algorithms can be used to provide remote monitoring of patients, alerting healthcare providers to changes in a patient's condition and enabling them to intervene in a timely manner (Alloghani, M et al., 2019).

Clinical decision support: AI algorithms can be used to assist healthcare providers in making more informed decisions about patient care, based on the analysis of large amounts of data.

Drug discovery: AI algorithms can be used to streamline the drug discovery process by helping to identify new targets for drug development and optimizing clinical trial design (Kulkov, I., 2021).

The integration of AI into the healthcare industry has the potential to improve patient outcomes, increase efficiency and reduce costs, and provide more personalized care to patients.

However, it is important to ensure that AI technologies are developed and implemented in a safe, effective, and responsible manner, considering ethical and legal considerations (Davenport, T., & Kalakota, R., 2019).

Benefits and Challenges of AI in Medicine

The benefits of AI in medicine are numerous, including increased accuracy and speed in diagnosing diseases, personalized treatment plans, and cost savings. However, there are also several challenges that need to be addressed, such as the need for large amounts of high-quality data, the potential for bias in AI algorithms, and the ethical and legal implications of using AI in medicine. Additionally, there is a need for further research and development to ensure the safe and effective integration of AI in the healthcare sector. Overall, the benefits of AI in medicine are clear, but the challenges must also be addressed to ensure the safe, effective, and responsible integration of AI into clinical practice. It is important to approach the development and implementation of AI in healthcare with caution, considering ethical and legal considerations and working to ensure that AI is used in a way that benefits patients and the wider healthcare system.

Benefits of AI in Medicine

Improved patient outcomes: AI has the potential to improve patient outcomes by enabling healthcare providers to make more informed decisions about patient care, based on the analysis of large amounts of data.

Increased efficiency: AI can help to streamline healthcare delivery by automating repetitive tasks, reducing wait times, and improving patient flow.

Personalized medicine: AI algorithms can be used to analyze a patient's genetic information, medical history, and other data to provide personalized recommendations for treatment and care, leading to improved patient outcomes (Albu, A., & Stanciu, L. , 2015).

Remote patient care: AI has the potential to improve remote patient care, enabling healthcare providers to reach patients in remote or underserved areas.

Clinical decision support: AI algorithms can be used to assist healthcare providers in making more informed decisions about patient care, based on the analysis of large amounts of data (Yeasmin, S. ,2019).

Challenges of AI in Medicine

Data privacy and security: The use of AI in healthcare requires access to large amounts of patient data, which raises concerns about data privacy and security.

Bias and fairness: There is a risk that AI algorithms used in healthcare may perpetuate existing biases, leading to unequal or unfair treatment for certain patient populations.

Integration into clinical practice: The integration of AI into clinical practice can be challenging, requiring significant changes to existing healthcare systems and processes (Yu, K. H., & Kohane, I. S., 2019).

Regulation and oversight: The development and implementation of AI technologies in healthcare is subject to a range of regulatory and ethical considerations, requiring careful oversight and management.

Cost: The development and implementation of AI technologies can be expensive, requiring significant investments in technology and infrastructure.

In conclusion, AI holds great promise for the future of medicine, but it is important to approach its implementation with caution and a clear understanding of the benefits and challenges it presents. With responsible and ethical development, AI has the potential to transform the way healthcare is delivered and improve patient outcomes (Guan, J., 2019).

Applications of AI in Medicine

AI is being applied in various areas of medicine to improve healthcare delivery and patient outcomes. Some of the key applications of AI in medicine include:

Diagnosis and Disease Detection: AI algorithms are being used to analyze medical images and support the diagnosis of diseases such as cancer, heart disease, and diabetic retinopathy. AI-powered tools can assist healthcare professionals in identifying abnormalities in images, such as X-rays, MRIs, and CT scans, that might be missed by human interpretation. IDx-DR, an AI-powered diagnostic tool for diabetic retinopathy, has been approved by the US Food and Drug Administration (FDA) for use in primary care settings (FDA-Cleared, 2023).

Personalized Medicine and Drug Discovery: AI is being used to analyze large amounts of genetic data to identify patient-specific genetic markers, which can then be used to personalize treatment plans. AI-powered drug discovery platforms are also being developed to identify new drugs and predict their efficacy, reducing the time and cost of the drug development process. Atomwise, a company that uses AI to predict the efficacy of new drugs, has been successful in identifying new treatments for a variety of diseases, including cancer and Alzheimer's (Atomwise, 2023).

Clinical Decision Support: AI algorithms are being integrated into electronic health record (EHR) systems to provide real-time decision support to healthcare professionals. AI algorithms can analyze patient data, including medical history, lab results, and vital signs, to provide personalized recommendations and treatment plans. Medgle, a platform that integrates AI algorithms into electronic health records (EHRs), provides real-time decision support to healthcare professionals (Medgle, 2023).

Healthcare Management and Administration: AI is being used to optimize healthcare processes, such as patient scheduling, resource allocation, and medical coding. AI algorithms can analyze large amounts of data to identify trends and patterns, helping healthcare organizations to improve operational efficiency and reduce costs. Optum, a subsidiary of UnitedHealth Group, uses AI algorithms to improve healthcare processes, such as medical coding and resource allocation (Optum Empowerin, 2023).

These examples and references provide a glimpse into the ways AI is being applied in the healthcare industry to improve the accuracy of diagnoses, personalize treatment plans, and optimize healthcare processes. As AI continues to evolve and become more integrated into healthcare, there will likely be even more innovative applications that emerge, further transforming the way healthcare is delivered. Overall, AI has the potential to transform the way healthcare is delivered, providing more accurate and efficient diagnoses, personalized treatment plans, and improved patient outcomes. However, it is important to approach the implementation of AI in medicine with caution, ensuring that AI algorithms are trained on high-quality data and that ethical and legal considerations are considered.

Table-1 Improvement fields of AI in medicine

Improvement	Description
Diagnosis	AI can help identify diseases and conditions with greater accuracy, speed, and efficiency than traditional methods. For example, machine learning algorithms can analyze medical images to detect patterns and anomalies that might not be visible to the human eye.
Treatment	AI can assist in developing personalized treatment plans for patients based on their unique characteristics, such as genetics, lifestyle, and medical history. This can lead to more targeted and effective treatments.
Drug discovery	AI can accelerate the process of drug discovery by analyzing large datasets of genetic and chemical information to identify promising drug candidates. This can potentially lead to the development of new and more effective drugs.
Clinical trials	AI can help improve the design and execution of clinical trials by identifying suitable patient populations, predicting outcomes, and optimizing trial protocols. This can reduce the time and cost of bringing new treatments to market.
Telemedicine	AI can facilitate remote diagnosis and treatment of patients through telemedicine technologies. For example, chatbots and virtual assistants can provide basic medical advice and guidance, while AI-powered diagnostic tools can analyze symptoms and recommend appropriate treatments.
Patient monitoring	AI can monitor patients in real time and alert healthcare providers to potential issues before they become serious. For example, wearable devices can track vital signs and activity levels, while machine learning algorithms can analyze data from electronic health records to identify patients at high risk of developing complications.

Ethical and Legal Issues in AI in Medicine

To address these ethical and legal issues, it is important to have a clear and transparent framework for the development and use of AI in medicine. This framework should address data privacy, bias and discrimination, responsibility and liability, autonomy and control, and transparency and interpretability, among other factors. Additionally, it is important to continuously monitor the performance and outcomes of AI algorithms and to address any issues that arise (Matsuzaki, T. ,2018).

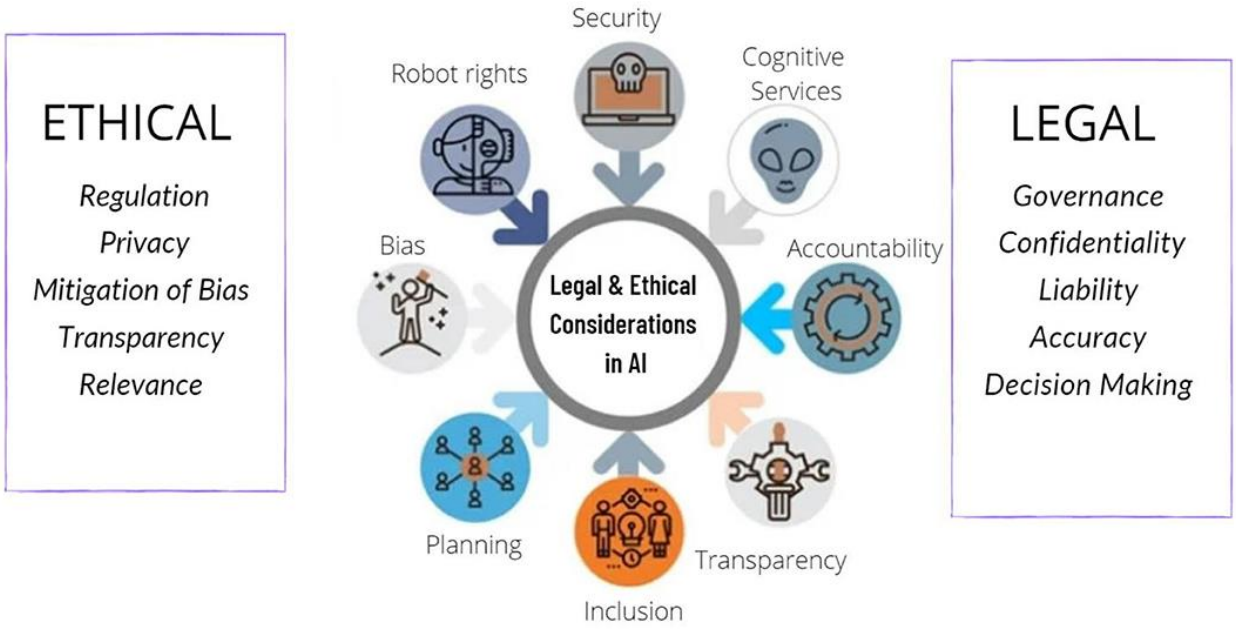

Figure-2 *Ethical and Legal issues of AI in medicine. (Naik, N., Hameed, et al., 2022)*

Ethical Issues in AI in Medicine

Bias and fairness: There are risks that AI algorithms used in healthcare may perpetuate existing biases, leading to unequal or unfair treatment for certain patient populations.

Data privacy and security: The use of AI in healthcare requires access to large amounts of patient data, which raises concerns about data privacy and security.

Autonomy and informed consent: There is a risk that the use of AI in healthcare may undermine patient autonomy and informed consent, as patients may not fully understand the implications of their data being used in this way.

Responsibility and accountability: The use of AI in healthcare raises questions about responsibility and accountability, as AI algorithms may not be fully transparent or may be influenced by factors beyond the control of healthcare providers.

Legal Issues in AI in Medicine

Data protection and privacy: The use of AI in healthcare is subject to data protection and privacy laws, including regulations such as the General Data Protection Regulation (GDPR) in Europe.

Liability: The use of AI in healthcare raises questions about liability, as healthcare providers may be held responsible for any harm caused by AI algorithms.

Intellectual property: The development and use of AI algorithms in healthcare raises questions about intellectual property rights, as AI algorithms may be subject to patent or trademark protection.

Regulation: The development and use of AI in healthcare is subject to a range of regulatory requirements, including those related to medical devices, data protection, and privacy.

Overall, it is essential that the ethical and legal issues surrounding AI in medicine are carefully considered and addressed to ensure that AI is used in a responsible and safe manner, with due respect for patient privacy, autonomy, and informed consent. This requires a

collaborative effort between healthcare providers, researchers, policy makers, and technology companies, to ensure that AI is developed and used in a way that benefits patients and the wider healthcare system. Here are some additional examples and details related to ethical and legal issues in AI in medicine (Price, I. I., & Nicholson, W. ,2017):

Bias and fairness: AI algorithms used in healthcare can be influenced by historical data and existing biases, leading to unequal or unfair treatment for certain patient populations. For example, a study found that a commercially available AI tool used to predict patient outcomes in hospitals was biased against black patients, leading to lower quality of care and worse health outcomes. To address this issue, it is important to ensure that AI algorithms are designed and tested to minimize bias and discrimination.

Data privacy and security: The use of AI in healthcare requires access to large amounts of patient data, which raises concerns about data privacy and security. For example, AI algorithms used in precision medicine may require access to sensitive personal information, such as genetic information, that can be used to identify individuals. To address these concerns, it is important to ensure that AI algorithms are designed to protect patient privacy and that data is securely stored and managed.

Autonomy and informed consent: The use of AI in healthcare may undermine patient autonomy and informed consent, as patients may not fully understand the implications of their data being used in this way. For example, patients may not be aware that their medical data is being used to train AI algorithms or that the results of an AI analysis may be used to make medical decisions. To address this issue, it is important to ensure that patients are fully informed about the use of AI in their care and that they can provide informed consent.

Responsibility and accountability: The use of AI in healthcare raises questions about responsibility and accountability, as AI algorithms may not be fully transparent or may be influenced by factors beyond the control of healthcare providers. For example, AI algorithms used in medical diagnosis may be based on proprietary data or models, making it difficult to understand how decisions are being made or to hold healthcare providers accountable. To address this issue, it is important to ensure that AI algorithms are transparent and that the decision-making processes used by AI are open and accessible for review and analysis.

Data protection and privacy: The use of AI in healthcare is subject to data protection and privacy laws, including regulations such as the General Data Protection Regulation (GDPR) in Europe. For example, under the GDPR, patients have the right to access and control their personal data, including data used to train AI algorithms. To address this issue, it is important to ensure that AI algorithms are designed to comply with data protection and privacy laws and that patients are able to exercise their rights with respect to their data.

Liability: The use of AI in healthcare raises questions about liability, as healthcare providers may be held responsible for any harm caused by AI algorithms. For example, if an AI algorithm used in medical diagnosis leads to a misdiagnosis or delay in treatment, the healthcare provider may be liable for any harm that results. To address this issue, it is important to ensure that AI algorithms are tested and validated before use and that appropriate liability provisions are in place to protect healthcare providers.

Intellectual property: The development and use of AI algorithms in healthcare raises questions about intellectual property rights, as AI algorithms may be subject to patent or trademark protection. For example, if an AI algorithm is patented, it may limit the ability of healthcare providers to use the technology or to build upon existing algorithms. To address this issue, it is important to ensure that AI algorithms are developed and used in a way that respects intellectual property rights and that appropriate licensing arrangements are in place.

These are just some of the ethical and legal issues that must be considered and addressed as AI continues to be integrated into healthcare. It is important to recognize that these issues are complex and interrelated.

In the field of medicine, the implementation of AI brings both benefits and challenges. While AI has the potential to improve healthcare delivery and outcomes, it also raises ethical and legal issues that must be carefully considered and addressed. Some of the key ethical and legal concerns surrounding AI in medicine include:

Data privacy and security: Patients' health data is highly sensitive information, and the use of AI in medicine requires the collection, storage, and analysis of vast amounts of data. There is a risk that this data could be misused or exploited, which would have serious consequences for patients.

Bias and discrimination: AI systems can reflect the biases and prejudices of their developers, which could result in discriminatory outcomes in healthcare. This is particularly concerning in the case of predictive algorithms, which could use biased data to make decisions about patient care.

Responsibility and accountability: In the event of an error or harm caused by an AI system, it may be unclear who is responsible and should be held accountable. This is an important issue that must be addressed to ensure that patients are protected and that healthcare providers are not unfairly held liable.

Autonomy and decision-making: AI systems have the potential to automate many aspects of healthcare delivery, including decision-making. While this could lead to improved efficiency and accuracy, it also raises questions about the role of human healthcare providers and the extent to which patients' autonomy is preserved.

These ethical and legal issues demonstrate the importance of responsible and ethical development and implementation of AI in medicine. It is crucial that the healthcare industry works closely with experts in ethics, law, and computer science to ensure that AI systems are developed in a way that protects patients and advances healthcare delivery and outcomes.

The Future of AI in Medicine

The integration of AI into the healthcare industry has the potential to transform the way healthcare is delivered, leading to improved patient outcomes and reduced costs. Some of the ways AI is expected to shape the future of medicine include (Malik, P., Pathania, M., & Rathaur, V. K., 2019):

Predictive Medicine: AI algorithms will be used to predict the likelihood of future health problems, allowing for earlier intervention and more proactive care. For example, AI algorithms may be used to predict the onset of chronic diseases, such as diabetes and heart disease, based on patient data, such as genetics and lifestyle. For instance, a company that uses AI algorithms to detect cancer at its earliest stages, has raised over $100 million in funding to bring its technology to market (Freenome, 2023).

Personalized Medicine: AI algorithms will be used to create customized treatment plans for individual patients based on their unique needs, including their genetics, lifestyle, and medical history. For example, AI algorithms may be used to predict the efficacy of different treatments for a particular patient, helping to ensure that they receive the most effective and personalized care. Natera, a company that uses AI algorithms to personalize cancer treatment, has received FDA clearance for its liquid biopsy test, which can identify the most effective treatment options for individual patients (Natera's Liquid Biopsy, 2023).

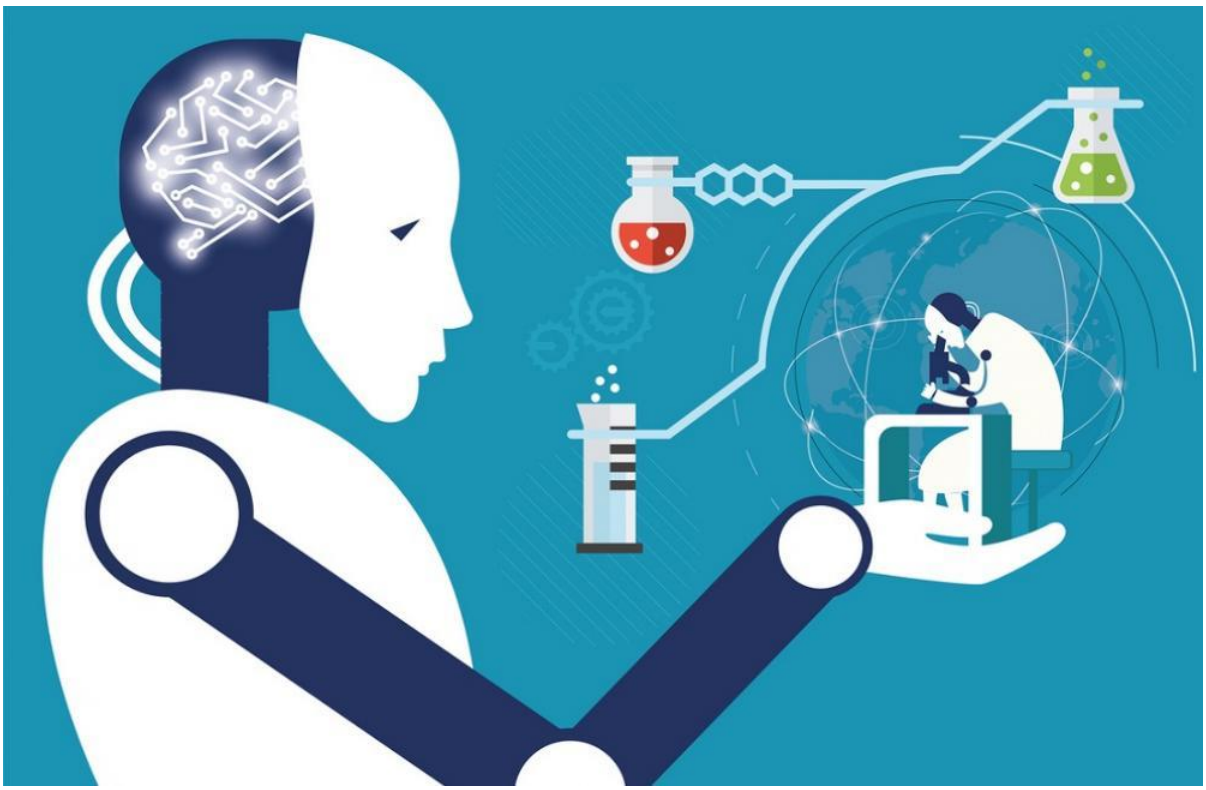

Figure-3 Future of AI in medicine. (infusedinnovations.com, 2023)

Improved Clinical Decision Making: AI algorithms will be integrated into electronic health records (EHRs) to provide real-time decision support to healthcare professionals. For example, AI algorithms may be used to identify the most appropriate treatment options for a patient based on their medical history, test results, and other factors. IBM Watson Health, a subsidiary of IBM, has developed AI algorithms that integrate into EHRs to provide real-time decision support to healthcare professionals (IBM Watson Health, 2023).

Telemedicine: AI algorithms will be used to support remote patient care and monitoring, enabling patients to receive care from the comfort of their own homes. For example, AI algorithms may be used to analyze patient data from wearable devices, such as fitness trackers, to monitor their health and detect early signs of problems. Teladoc Health, a telemedicine company that uses AI algorithms to support remote patient care and monitoring, has become one of the largest telemedicine companies in the world, providing access to healthcare for millions of patients globally (Teladoc Health, 2023).

Enhanced Drug Discovery and Development: AI algorithms will be used to speed up the drug discovery and development process, leading to the development of new treatments for a variety of diseases. For example, AI algorithms may be used to identify new drug targets and predict the efficacy of new drugs, helping to bring treatments to market faster and more efficiently. Atomwise, a company that uses AI algorithms to speed up the drug discovery and development process, has raised over $170 million in funding to bring its technology to market (Atomwise, 2023).

While these are just a few of the ways AI is expected to shape the future of medicine, AI has the potential to revolutionize the healthcare industry, leading to improved patient outcomes and a more efficient and effective healthcare system.

Advancements in AI technology In Medicine

Advancements in AI technology are leading to exciting developments in the field of medicine, enabling new and innovative solutions to some of the most pressing challenges in healthcare. Some of the key advancements in AI technology for medicine include:

Precision Medicine: AI algorithms are being used to analyze large amounts of medical data, including genomic data, to provide more personalized and accurate diagnoses and treatments for patients. Foundation Medicine, a company that provides genomic analysis to help inform cancer treatment, has raised over $400 million in funding to bring its technology to market (Foundation Medicine, 2023).

Clinical Decision Support Systems: AI algorithms are being used to support clinical decision making by analyzing medical data, including electronic health records, to provide insights and recommendations to healthcare professionals. : IDx, a company that provides AI-powered clinical decision support systems for the early detection of diseases, has received FDA approval for its first product, IDx-DR, which uses AI to detect diabetic retinopathy (IDx, 2023).

Medical Imaging: AI algorithms are being used to analyze medical images, such as X-rays, MRI scans, and CT scans, to help diagnose and monitor diseases and conditions. : Zebra Medical Vision, a company that provides AI-powered medical imaging solutions, has raised over $30 million in funding to bring its technology to market (Zebra Medical Vision, 2023).

Diagnosis and Treatment Planning: AI algorithms are being used to diagnose diseases and conditions and to help plan treatments based on a patient's individual needs and medical history. Enlitic, a company that provides AI-powered medical imaging solutions for diagnosis and treatment planning, has raised over $50 million in funding to bring its technology to market (Enlitic, 2023).

Drug Discovery and Development: AI algorithms are being used to speed up the drug discovery and development process, including the identification of new targets for drug development, the design of new drugs, and the prediction of drug efficacy and toxicity. Atomwise, a company that uses AI algorithms to speed up the drug discovery and development process, has raised over $170 million in funding to bring its technology to market (Atomwise, 2023).

These advancements in AI technology for medicine are providing new and innovative solutions to some of the most pressing challenges in healthcare, including improving patient outcomes, reducing costs, and increasing access to care.

Integration of AI in clinical practice in medicine

The integration of AI in clinical practice in medicine is a rapidly evolving field, with healthcare professionals, researchers, and technology companies exploring new and innovative ways to use AI to improve patient care. Some of the key considerations and challenges in integrating AI into clinical practice include:

Clinical Workflow Integration: One of the biggest challenges in integrating AI into clinical practice is ensuring that AI algorithms fit seamlessly into existing clinical workflows and processes. iSchemaView, a company that provides AI-powered solutions for clinical workflow integration, has raised over $40 million in funding to bring its technology to market (Atomwise , 2023).

Data Privacy and Security: The integration of AI into clinical practice requires large amounts of medical data, which must be kept secure and confidential to protect patients' privacy. Cylera, a company that provides AI-powered solutions for data privacy and security in

healthcare, has raised over $20 million in funding to bring its technology to market (iSchemaView, 2022).

Regulation and Standardization: There is a need for regulation and standardization in the use of AI in medicine to ensure that AI algorithms are safe, effective, and unbiased. The US Food and Drug Administration (FDA) has established a regulatory framework for the use of AI in medical devices, including a premarket review process for new AI-powered medical devices (FDA, 2023).

Interoperability: To provide the best possible care, AI algorithms must be able to seamlessly exchange and integrate data with other medical systems, including electronic health records and medical imaging systems. Freenome, a company that provides AI-powered solutions for cancer screening and diagnosis, has raised over $300 million in funding to bring its technology to market ().

Clinical Validation and Adoption: The integration of AI into clinical practice requires rigorous clinical validation and testing to ensure that AI algorithms are safe, effective, and provide meaningful improvements to patient care.

Despite these challenges, the integration of AI into clinical practice in medicine holds great promise for improving patient outcomes, reducing costs, and increasing access to care. In order to maximize the benefits of AI in medicine, it will be important for healthcare professionals, researchers, and technology companies to work together to ensure that AI algorithms are integrated into clinical practice in a safe, effective, and responsible manner.

Conclusion about AI in medicine

In conclusion, AI has the potential to revolutionize the field of medicine, leading to major improvements in patient outcomes and healthcare delivery. With advancements in AI technology, it is becoming increasingly clear that AI will play a critical role in the future of healthcare. However, to fully realize the potential impact of AI on healthcare delivery and outcomes, it will be important for healthcare professionals, researchers, and technology companies to work together to ensure that AI algorithms are developed and integrated into clinical practice in a safe, effective, and responsible manner. The future of AI in medicine is promising, and there is no doubt that AI will play a key role in shaping the way healthcare is delivered in the years to come. The current state of AI in medicine is in a state of rapid growth and development, with AI technologies becoming increasingly sophisticated and capable of providing powerful solutions for a wide range of medical problems. AI algorithms are already being used in areas such as medical imaging analysis, personalized medicine, and remote patient care, and there is a growing body of evidence to suggest that AI has the potential to revolutionize the way healthcare is delivered. However, despite these promising developments, there are also challenges and risks associated with the use of AI in healthcare, including data privacy and security, potential biases in AI algorithms, and regulatory challenges. To ensure that AI technologies are developed and integrated into clinical practice in a safe, effective, and responsible manner, it will be important for healthcare professionals, researchers, and technology companies to work together to address these challenges and to ensure that patients and healthcare providers realize the benefits of AI alike.

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Bıoactıve Glass Materıals In Dentıstry

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Introduction

Biomaterials are materials used in the production of devices intended to safely, reliably, economically, and physiologically acceptably replace a part or function of the body. Over the years, various definitions have been proposed for the term biomaterials. For instance, a biomaterial can simply be defined as a synthetic material used to replace a part of a living system or work in close contact with living tissues. Biomaterials can be examined in four different groups. These are metals, ceramics, polymers, and composites. Within the ceramics group, there are three groups according to tissue interactions: those that are resorbable, those that are inert, and those that are bioactive. Bioactive glasses (BAG) are a member of the bioactive group within ceramics (Al-Mayyahi & Izman, 2015).

The bonding of 45S5 Bioglass to bone was discovered at the University of Florida in 1969, and in 1985, the first medical product, "Bioglass Bone Reconstruction Prosthesis", was approved by the FDA (Karasu et al., 2017). The Bioglass concept was based on a simple hypothesis: 'The human body rejects metallic and synthetic polymeric materials by forming scar tissue because living tissues do not consist of such materials. Bone contains hydroxyapatite ; therefore, if a material can form a hydroxyapatite layer in vivo, it cannot be rejected by the body (Hench et al., 2004). The advantage of 45S5 is that it tends not to form fibrous tissue (Nicholson, 2020). Bioactive glasses are considered to be osteoconductive and osteoinductive (Rezwan et al., 2006).

Composition of Bioactive Glass Materials

The structure of BAG significantly influences its bonding mechanism. The basic structure of BAG is composed of silica. The structure is water-soluble due to the presence of sodium and calcium ions(Sawant & Pawar, 2020). Bioglass® 45S5 contains 45% SiO_2, 24.5% Na_2O, 24.5% CaO, and 6% P_2O_5 (Hench et al., 2004). BAG consists of 2 main classes, namely class A and B. Class A BAGs are reported to predominantly contain 40-52% SiO_2, 10-50% CaO, and 10-35% Na_2O. Additionally, the glass composition may contain 2-8% P_2O_5, 0-25% CaF_2, or 0-10% B_2O_3. Class B glasses generally contain bio-inert high silica (>60% by mass)(El-Meliegy & Van Noort, 2011). BAG may also contain bio-compatible and bioactive minerals, including fluorapatite (FAP), wollastonite, diopside, and tricalcium phosphate (Ferreira et al., 2018; Lowe et al., 2019). Non-alkaline (particularly Na-free) BAG contains 70% diopside, 10% fluorapatite, and 20% tricalcium phosphate and is commercially known as FastOs® BAG. Network modifiers CaO, Na_2O, and P_2O_5 can be added to the elemental Na_2O-CaO-SiO_2

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composition to make the surface and silica network more reactive (Rodriguez et al., 2018; Skallevold et al., 2019).

The addition of fluoride to bioactive glass has been reported to reduce the hardness of the glass and enhance its bioactivity (Brauer et al., 2009). Fluoride prevents demineralization and enhances remineralization. The role of fluoride in preventing caries is significant because it replaces hydroxyl ions in the apatite structure, forming fluorapatite (Farooq et al., 2012).

Types of Bioactive Glass Materials

There have been many variations on the original composition known as Bioglass, approved by the Food and Drug Administration (FDA). This composition is known as Bioglass 45S5. Some other names for BAG include S53P4, 58S, 70S30C, and 13-93 (Bui & Dang, 2019; Elhamouly et al., 2021; Hench & Jones, 2015; Liu et al., 2013).

The S53P4 bioactive glass is based on BAG 45S5 developed by Larry Hench in New York in the late 1960s. In the 1980s, the S53P4 bioactive glass compound was developed in Finland (Ltd., 2020). The first 45S5 non-composition in the market is S53P4, now known as BonAlive® (BonAlive Biomaterials, Turku, Finland) (Hench & Jones, 2015).

S53P4 was found to be osteostimulative, but it also had an additional feature: the 53% silica composition and lower weight of sodium, calcium, and phosphorus led to surface reactions that were seen to inhibit bacterial growth in vitro, and it was discovered to be a material that could not be infected by bacteria (Ltd., 2020). S53P4 is osteoconductive and also osteoproductive in supporting, migrating, replicating, and differentiating osteogenic cells and their matrix production. That is, it has facilitated the bone formation and regeneration (osteostimulation) (Virolainen et al., 1997).

In a multicentric study, 11 patients with chronic osteomyelitis in the lower extremity and spine were treated with BAG-S53P4 as a bone substitute. In the study with an average follow-up period of 24 months, 9 patients recovered without complications (Fig.1) (Lindfors et al., 2010).

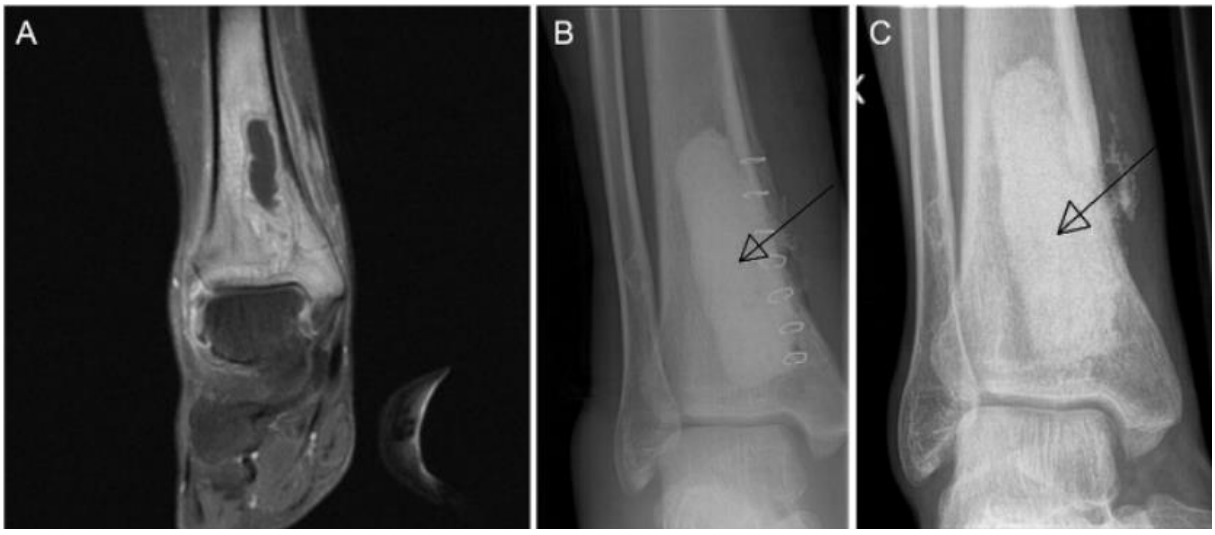

Figure 1. (A–C) Osteomyelitis caused by S. aureus in the distal tibia treated with BAG-S53P4 as a bone graft: (A) preoperative MRI showing osteomyelitis in the tibia, (B) postoperative X-ray showing BAG-S53P4. S53P4 (arrow) in the treated bone void and (C) X-ray showing the treated region (arrow) at a five-month follow-up (Lindfors et al., 2010).

Production Methods of Bioactive Glass Materials

For years, traditional glass technology has been used to produce bioactive glass. Oxide or carbonate grains are mixed as glass components and homogenized at high temperatures (up to 1250-1400°C) by placing them in a platinum container. Then, the molten glass is poured into steel or a graphite mold. Due to disadvantages such as failure to achieve optimal bioactivity and increased costs, this method has been abandoned (Abbasi et al., 2015). The low-temperature sol-gel process offers a suitable alternative to the traditional glass process by significantly reducing costs by lowering process temperatures (Li et al., 1991). Sol-gel is a term derived from the combination of "solution-gelation"; it is a solution-gelation method (Ceyhan et al., 2007). The sol-gel method is a wet-chemical process used to produce materials from building blocks such as metal ions and silicate tetrahedra in bioactive glasses (Brinker & Scherer, 2013). This process essentially involves the hydrolysis and condensation of precursors, drying, and stabilization steps. Features such as the properties, morphology, and composition of the materials can be controlled by controlling process parameters. Tetraethyl orthosilicate (TEOS) is the most commonly used material as a silicate precursor for the sol-gel synthesis of bioactive glass, and water and/or ethanol are used as a solvent (Zheng & Boccaccini, 2017). In the sol-gel process, many disadvantages of the traditional method can be eliminated and the purity resulting from processing at low temperatures (600-700°C) can be controlled. The advantages of this method include ease of powder production, a wider range of bioactivity and better control, high homogeneity, easy control of particle size and morphology, and easy preparation of thin films and coatings (Abbasi et al., 2015).

Reactions Caused by Bioactive Glass Material

When bioactive glass material is applied, reactions begin on the surface of the material. These reactions can be examined in 3 main phases: the dissolution and exchange of cations, the dispersion of SiO_2, and the precipitation of calcium and phosphate to form an apatite layer (Alauddin, 2004).

The reactions that occur on the Bioglass surface are as follows: Formation of Na^+ and silanol (SiOH) ions, dissolution of silica on the surface and formation of Si-O-Si bonds, precipitation of amorphous calcium phosphate, nucleation and crystallization of calcium phosphate into HCA, the capture of biological particles (protein, etc.), movement of macrophages, attachment of body cells, change of body cells, formation of the matrix, and finally the crystallization of the matrix (Kükürtcü, 2008).

Antibacterial Effect

The antimicrobial effect of bioactive glasses is formed thanks to the increase in the pH of the environment and the resistance of the material to biofilm formation (Allan et al., 2001). In a study evaluating biofilm removal efficacy using scanning electron microscope (SEM) imaging and culture techniques, air abrasion with 45S5 BAG or Zn4 BAG showed a significant decrease in the number of live bacteria compared to biofilms preserved without inert glass or abrasion. Moreover, P. gingivalis could not be detected in SEM images or culture plates after air abrasion with 45S5 BAG or Zn4 BAG. This study demonstrated the effect of air abrasion with 45S5 or Zn4 bioactive glasses, which can successfully eradicate F. nucleatum and P. gingivalis dual-biofilms on sandblasted and acid-etched titanium disks (Abushahba et al., 2021).

One of the key features of bioactive glasses is their ability to demonstrate antibacterial activity while repairing the defect region. This antibacterial effect can be particularly beneficial in persistent root canal infections and regenerative endodontic treatments (Alim Uysal, 2020).

Moreover, a study conducted on bioglass supplemented with lithium found that the presence of lithium did not affect the bioactivity of the bioglass, but it enhanced its antibacterial effect against A. actinomycetemcomitans strain (Cordero et al., 2021).

Given that alkalinity is regarded as the primary antimicrobial mechanism, Bioglass® 45S5 is considered more effective (Vallittu et al., 2015). The U.S. Food and Drug Administration (FDA) has approved Bioglass® 45S5 and S53P4 for clinical applications where antimicrobial properties are desired (Vallittu, 2017).

Application of Bioactive Glass Materials

Bioactive glasses can adhere to both soft and hard tissue and can promote bone growth. The bioactivity behavior of these glasses is related to the biologically active hydroxyapatite layer that forms on their surfaces (Alim Uysal, 2020). In this way, bioactive glasses have the potential to be used in various fields of dentistry. These applications include the treatment of sensitivity after whitening (Bizreh & Milly, 2022) dentin sensitivity treatment (Burwell et al., 2010; Jafari et al., 2022), air abrasion, restorative materials, vital pulp treatments and root canal treatment, bone regeneration, periodontology, implant treatment, maxillofacial surgery, dental adhesives, and enamel remineralization. These applications are illustrated in Figure 2 (Skallevold et al., 2019).

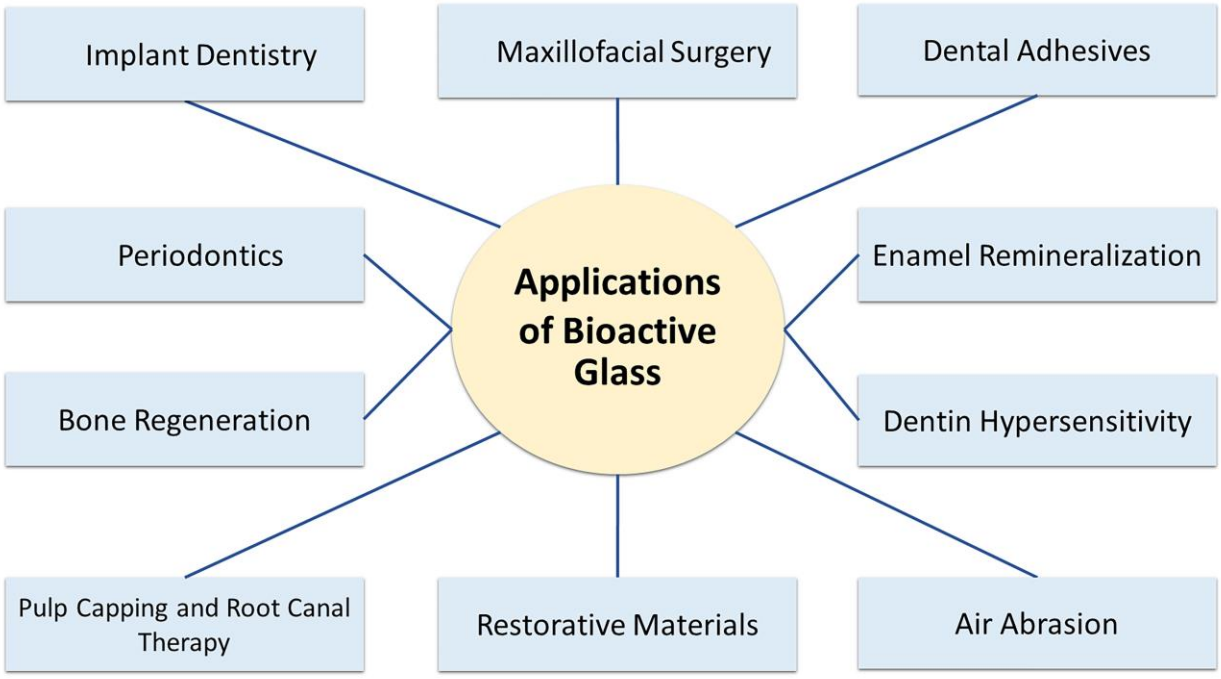

Figure 2. Bioactive Glass Applications (Skallevold et al., 2019)

Sensitivity Treatment

Dentin sensitivity is a "short and painful discomfort arising from exposed dentin, typically as a response to thermal, physical, osmotic, or chemical stimuli, and which cannot be ascribed to any other dental disorder or disease" (Holland et al., 1997). The theory accepted as the pain-generation mechanism of DH is the "hydrodynamic theory". When the extracellular fluid in the dentin tubules moves, the odontoblasts can perceive this movement. Since odontoblasts are in close contact with the afferent pain nerve fibers in the tubules, they can transmit the sensation

of pain. The movement of the fluid can be caused by drying, thermal changes (hot and cold), physical force (nail or tooth probing tool), or osmotic pressures (dissolution of sugars) (Limeback et al., 2023).

According to the hydrodynamic theory, dentin sensitivity pain can be reduced by blocking nerve endings or closing dentin tubules. Bioactive glasses can alleviate pain during dentin sensitivity by forming a hydroxyapatite reservoir to block the dentin tubules and by binding to collagen fibers (Jafari et al., 2022).

One of the commercial bioactive glasses used in the treatment of dental hypersensitivity and enamel remineralization is NovaMin. NovaMin is a ceramic material composed of amorphous sodium-calcium-phosphosilicate, which is highly reactive in water, and it consists of a finely particulate powder capable of physically blocking dentin tubules (Gjorgievska & Nicholson, 2011). NovaMin is used as an active repair agent in toothpaste. (Tai et al., 2006). In the aqueous environment of the tooth, sodium ions from NovaMin particles rapidly exchange places with hydrogen cations (in the form of H_3O^+), which leads to the release of calcium and phosphate (PO_4^{3-}). During the material's initial exposure to water, a localized, temporary increase in pH occurs due to the release of sodium. This increase in pH aids in the precipitation of additional calcium and phosphate ions provided by NovaMin, forming a calcium phosphate layer. As these reactions continue, this layer crystallizes into hydroxyapatite enriched with carbonate (HCA). The combination of residual NovaMin particles and the newly formed HCA layer causes the remineralization of the enamel surface and prevents further demineralization (Gjorgievska & Nicholson, 2011). In summary, NovaMin adheres to an open dentin surface and facilitates the formation of a mineralized layer. The resulting layer is acid-resistant and mechanically strong. Over time, the continuous release of calcium maintains protective effects on dentin and ensures the ongoing sealing of dentin tubules. The blockage of dentin tubules reduces tooth sensitivity (Burwell et al., 2010).

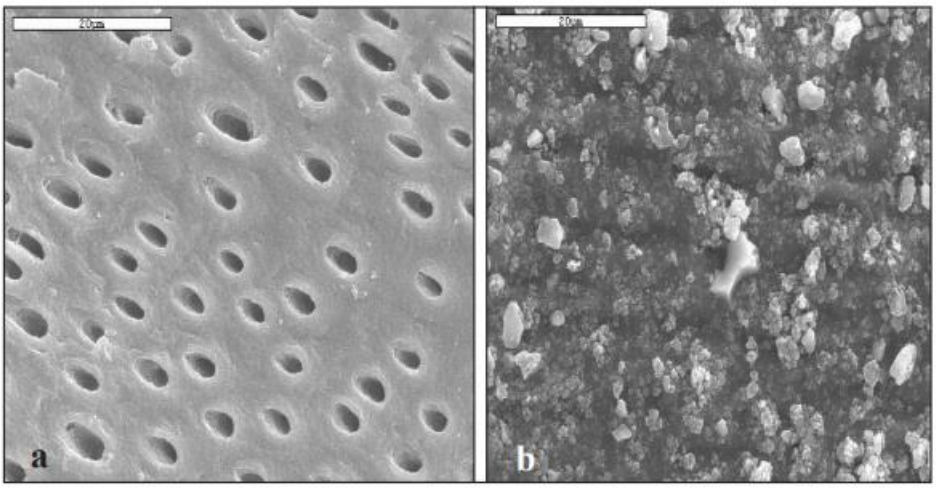

Figure 3. a. SEM image of a prepared dentin sample showing open tubules. b. SEM image of a dentin sample after a two-minute application of NovaMin and a 30-second water rinse (Banerjee et al., 2010).

The SEM image in Figure 3a shows a polished dentin sample that has been acidified to remove the smear layer and to expose open tubules. Figure 3b displays a dentin block that has been treated once with NovaMin material and then exposed to acid. After the acid application, the sample is gently rinsed and dried for SEM analysis. The majority of the tubules appear completely closed, and the remainder are at least partially closed. Interestingly, even after the rinsing process, particles remain on the surface of the dentin block. This evidence confirms the long-term effect of even a single use of NovaMin particles (Banerjee et al., 2010).

NovaMin adheres to the dentin surface and interacts with it to form a mineralized layer. The formed layer is resistant to acid attacks and is mechanically strong. Over time, the continuous release of calcium is thought to help maintain protective effects on the dentin and ensure ongoing tubule occlusion (Banerjee et al., 2010).

Salian et al. reported that toothpaste containing 5% novamin reduced dentin sensitivity and also was effective in plugging dentin tubules in their in vitro study (Fig 4) (Salian et al., 2010)

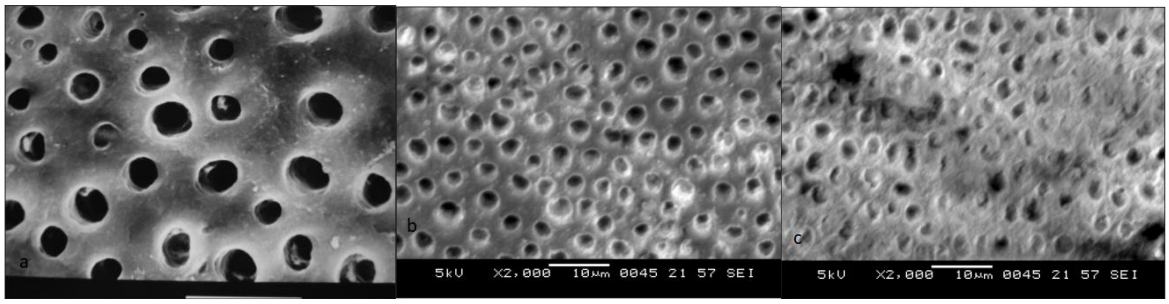

Figure 4. a. SEM image of a dentin sample with applied control toothpaste. b. SEM image of a dentin sample 10 minutes after application of a 5% NovaMin toothpaste. c. SEM image of a dentin sample 120 minutes after application of a 5% NovaMin toothpaste (Salian et al., 2010).

In a study comparing toothpaste containing NovaMin with stannous fluoride gel and potassium nitrate toothpaste, these three products showed significantly reduced sensitivity compared to initial dentin sensitivity. However, toothpaste containing calcium sodium phosphosilicate (NovaMin) reduced sensitivity more than the others after two and four weeks of use. In this study, all three products were found effective, but it was indicated that toothpaste containing NovaMin provided more improvement at an early stage compared to the formulations of potassium nitrate and stannous flüoride (Sharma et al., 2010).

BiominF, on the other hand, is another bioactive glass product used in toothpastes, with an active ingredient of fluoro-calcium-phospho-silicate (FCPS) (Arshad et al., 2021). It enables the formation of fluorapatite (Brauer et al., 2010). In 2021, Dr. Collins announced that his toothpaste containing BioMin had received FDA approval (Plus & has announced that BioMin, 2021). This toothpaste controls the release of calcium, phosphate, and fluoride ions for hours after brushing to enable the formation of acid-resistant fluorapatite on the tooth surface and within open dentin tubules (Plus & has announced that BioMin, 2021). At the same time, the dispersion of Biosilicate®, another bioactive glass, in distilled water is effective in treating dentin sensitivity and provides comfort over a 6-month follow-up period (Skallevold et al., 2019). Furthermore, bioactive glass-based desensitizers have been observed to create similar effects to products available on the market in terms of permeability and dentin biological characteristics (de Oliveira Reis et al., 2021).

Another study investigated the effect of bioactive glass on effectiveness and sensitivity after a home whitening procedure using 20% carbamide peroxide. It was concluded that the group using bioactive glass demonstrated less post-procedure sensitivity compared to the control group, without reducing the whitening effect (Bizreh & Milly, 2022).

Remineralization

The balance of remineralization and demineralization is disrupted due to increased intake of acidic and sugary foods. Even though enamel is the hardest tissue in the body, it can demineralize. On the other hand, antibacterial agents, saliva, and ions (e.g., fluoride, calcium,

and phosphate) promote remineralization. If this balance is disturbed over a long period, early tooth decay usually occurs (Salinovic et al., 2021). Early tooth decay leads to mineral loss in the lower layers of teeth and appears as an opaque, white area that continues after treatment. These lesions, called white spots, are considered reversible until surface cavitation occurs (Salah et al., 2022). Until now, the treatment modality for carious teeth has been the removal of decay and restoration. The approach of minimally invasive dentistry encourages the early identification and treatment of lesions, focusing on prevention (Rahiotis & Vougiouklakis, 2007).

Minimally invasive dentistry includes procedures to prevent maximum destruction of tooth tissue. One such modality is the remineralization of non-cavitated lesions without the need for conventional treatment. Remineralization agents, casein phosphopeptide-amorphous calcium phosphate, and bioactive glass have been used for enamel remineralization, and satisfactory results have been achieved (Bhavsar et al., 2022).

A recent study evaluating the effectiveness between bioactive glasses (45S5) and casein-phosphopeptide stabilized amorphous calcium phosphate (CPP-ACP) in the treatment of white lesions formed after orthodontic treatment found greater aesthetic improvements with 4 weeks of combined in-office and at-home application of BiominF paste compared to Novamin and CPP-ACP (Salah et al., 2022).

Dental Adhesives

Adhesion refers to the attachment resulting from the chemical or physical force between two different surfaces with the help of an adhesive (Berkmen et al., 2019). Dental adhesives are used for attachment to tooth tissue and, specifically, secure the attachment of composite resins to tooth tissue. Thus, more conservative dental restorations can be made instead of amalgam restorations (Kazak & Dönmez, 2019). The adhesive systems to be used should be chosen considering the structure of the remaining tooth tissue after the removal of the carious tooth tissue, their effects on the tooth tissue, and their biocompatibility (Berkmen et al., 2019). As dentin bonding systems and application techniques develop, these systems have become usable in many areas of dentistry (Kazak & Dönmez, 2019). Many studies are currently being conducted for the development of new adhesive systems (Berkmen et al., 2019).

Bonding systems containing bioactive glass, compared to systems not containing bioactive glass, can remineralize areas lacking minerals, reduce microleakage, and increase elasticity and hardness properties at the dentin interface (Sauro et al., 2012).

In a study, the silanized version of 45S5 bioglass added to the universal bond was found to be advantageous in terms of dentin remineralization, bonding performance, and adhesive polymerization (Rifane et al., 2023).

There is also a study finding that adding bioactive glass to the primary component of the adhesive did not affect bonding strength according to 1-week and 6-month results (Magne & Ubaldini, 2020).

Another study has examined the short and long-term dentin bond strength of the addition of different concentrations of nano-sized bioactive glasses (5, 10, and 20 %) to etch-and-rinse and self-etch adhesives. It was found that etch-and-rinse adhesives can be functionalized with 5% or 10% nano-sized bioactive glass without causing a negative impact on tooth-dentin bond strength, while adding bioactive glass to self-etch adhesive significantly reduced its performance for all bioactive glass concentrations, though a beneficial effect was found in terms of preserving dentin bond strength during a 6-month aging period (Magne & Ubaldini, 2020).

Restorative Materials

Current resin composites, having appropriate mechanical properties and excellent aesthetic characteristics, are materials preferred for numerous indications in dentistry. Despite all advancements, a significant unresolved deficiency is the high risk of secondary caries at the tooth/restoration border. This boundary cannot be sealed hermetically because polymerization shrinkage occurs, leading to the formation of secondary caries. A study examined the effects of functionalizing resin composites with conventional bioactive glass 45S5 and special bioactive glass with low Na F, comparing the level of deterioration of mechanical properties and the effects of aging. The study showed that the special bioactive glass degraded the mechanical properties less and decreased the rate of degradation of mechanical properties with aging (Par et al., 2022).

Experimental pit and fissure sealant materials (0-50 wt% BAG) showed a decrease in flexural strength and an increase in water absorption as the BAG content increased (Yang et al., 2013).

In another study, an Al-free 45S5 Bioglass® based GIC, comparable in compressive strength to commercially available glass ionomer cements, was developed. It was shown that the cement with solid components containing 50 wt% Bioglass® and 50 wt% bioceramics (74% crystalline) exhibited the highest combination of compressive strength and microhardness (Zandi Karimi et al., 2021).

In a study conducted at a point of the mine that is not immediately adjacent to the restoration, which investigates the anti-demineralization protective effect of experimental and commercial restorative materials with functional fillers, it was found that the protective and alkalinization effects of experimental composites improved with the increase of bioactive glass amount and conventional bioactive glass 45S5 gave better results than chloride-containing bioactive glass (Par et al., 2021).

Air Abrasion

In recent years, bioactive glasses have been discovered as a potential solution for minimally invasive dentistry. These glasses are less invasive than traditional methods used in the treatment of decayed teeth and result in less tooth material loss. Air abrasion is a common method for applying bioactive glasses to the tooth surface. This process uses a high-pressure jet to remove decayed tooth tissue using an air stream and a fine powder flow. When bioactive glasses are applied to the tooth surface during this process, they can provide remineralization in tooth enamel. Therefore, using bioactive glasses in minimally invasive dental treatment using air abrasion can help dentists remove decay with a less invasive method and preserve the natural structures of the teeth (Banerjee et al., 2011).

In a study comparing the use of bioactive glass powder and sodium bicarbonate in air abrasion, while bioactive glass powder has a longer-term sensitivity-reducing effect, sodium bicarbonate powders tend to increase dentin sensitivity. Therefore, bioactive glass powder offers a more acceptable clinical experience for professional tooth stain cleaning, and it has been stated that it may provide a significant additional benefit in reducing tooth sensitivity (Banerjee et al., 2010).

In another study where teeth were primarily pre-treated with air abrasion and then the enamel surface loss was measured by applying acid, it was found that the teeth pre-treated with bioactive glass air abrasion had less enamel surface loss compared to the other groups. As a result, pre-treatment of enamel surface with air abrasion with bioactive glass 45S5 could help protect the enamel surface after the effect of erosion/abrasion (Dionysopoulos et al., 2019).

It has been stated that applying air abrasion with bioactive glass as a pre-treatment to dentin could be a suitable strategy to enhance the bond performance and durability of resin-modified glass ionomer applied to dentin (Sauro et al., 2018).

In a study where implants were placed in the femur bones of rats and defects were created in the surrounding bone tissue, the contaminated surfaces around these implants were air-abraded with bioactive glass. The results showed that bioactive glass air abrasion promoted the healing of contaminated implant surfaces and improved the surrounding bone defects (Abushahba et al., 2023).

One of the bioactive glass powders used with air abrasion, Sylc®, allows the blockage of tubules, the formation of calcium phosphate islets, and spread at the dentin border (Sauro, Thompson, et al., 2011). Novamin, the active ingredient of Sylc®, reacts with the saliva environment, causing the release of calcium and phosphate ions (Burwell et al., 2009). When compared to other test materials (Prophy Powder and EMS Perio), it was observed that Sylc® bioactive glass facilitated the formation of hydroxycarbonate apatite by Raman spectroscopy and scanning electron microscopy (SEM) thereby providing remineralization (Fig 5) (Sauro, Thompson, et al., 2011).

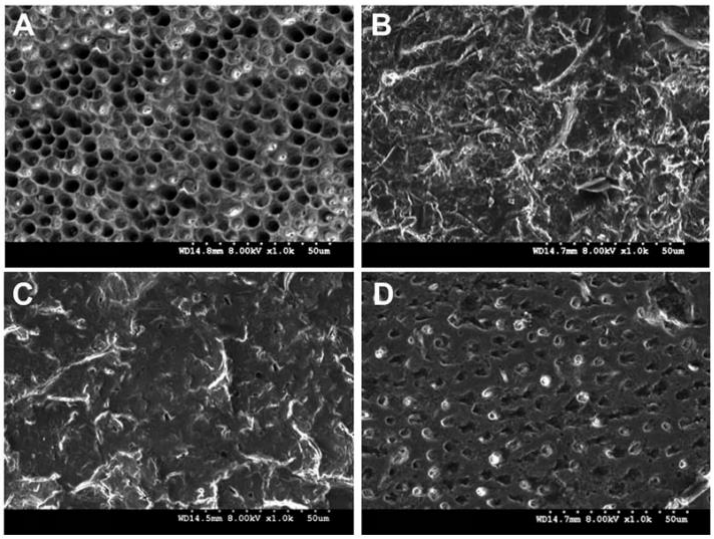

Figure 5. 1000X SEM micrographs of dentin surfaces on which air abrasion was applied using the prophylaxis powders tested in this study. A) It shows the effects of H_3PO_4 on the dentin surface and leads to fully opened dentinal tubules. B) It shows the effects of Sylc® bioactive glass powder on the dentin surface. This process creates a multilayer smear layer that blocks the dentinal tubules. C) Show the effects of Prophy-Jet sodium bicarbonate powder on the dentin surface, and this process also shows the creation of a smear layer that covers the dentin surface and blocks the dentinal tubules. D) It shows the effects of EMS Perio powder on the dentin surface and leads to fully or partially opened tubules (Sauro, Thompson, et al., 2011).

In a study examining the effect of caries removal methods on the micro-tensile bond strength, after the use of tungsten carbide bur in caries removal, bioactive glass particles were applied to the dentin surface with 4 bar pressure. Applying bioactive glass to the dentin surface did not cause a negative effect on dentin bonding, showing similar results with the use of ceramic bur (Kanar, 2022).

In a study where prophylactic pastes and air polishing powders were tested, a quantitative decrease in dentin permeability under pulpal pressure (20 cm H_2O) was examined in dentin samples taken from human third molar teeth. Depending on the type of product used (i.e.,

prophylactic paste or air polishing powders), different decreases in dentin permeability were observed Sylc® bioactive glass and sodium bicarbonate were the 2 most effective materials in reducing the dentin permeability of the samples. While all the products tested can statistically reduce dentin permeability, it was concluded that Sylc® bioactive glass is an innovative and effective product that completely blocks dentinal tubules during air abrasion procedures (Sauro, Watson, et al., 2011).

Vital Pulp Therapies and Root Canal Treatment

In dental pulp disorders, there are various treatment options such as pulpectomy, pulpotomy, and pulp capping, and the materials that can be used in these treatments play a very effective role in terms of the prognosis of the teeth and the success of the treatment (Hilton, 2009). In a study conducted on rats, a new glass showing a biological effect was used as a pulp capping material after direct pulp capping. The results showed that bioactive glass stimulated the formation of dense dentin bridges with inflammatory reactions similar to mineral trioxide aggregate (MTA) (Long et al., 2017). It was stated that bioactive glasses play an effective role among the materials that can be used in pulp inflammation and have antimicrobial effects (Jafari et al., 2022).

A pulp capping material should provide a tight seal, and be biocompatible, antibacterial, and easy to use. Also, it should encourage the formation of a dentin bridge to protect the pulp. Although the dentin bridge caused by calcium hydroxide is deficient due to tunnel-like defects, it has been used in various endodontic applications such as pulp capping. The long curing time and delicate use during application are other major disadvantages of calcium hydroxide (Macwan & Deshpande, 2014). Bioactive glass (BAG) has been investigated for pulp capping due to its dentin formation properties. An in-vitro study demonstrated that ions released from sol-gel nanoporous BAG particles did not inhibit the growth of human dental pulp stem cells (hDPSCs), but did show high-density mineralized nodules (Gholami et al., 2017).

Resilon (Resilon Research LLC, Madison, CT, USA) is a root canal-filling material containing bioactive glass (Elzubair et al., 2006). The filler in Resilon includes bioactive glass, calcium-rich hydroxyapatite, silica, bismuth oxychloride, zirconium oxide, barium oxide, barium sulfate, and cerium phosphate (Kaya & Keçeci, 2008). BioGutta (smartodont llc), on the other hand, is an antibacterial and leak-proof gutta-percha containing 45S5 (Wu et al., 2000). BioGutta is a highly biocompatible sealing material (Alim Uysal, 2020).

When experimental endodontic sealer materials containing bioactive glass were examined, it was concluded that despite showing bioactive properties, their solubility characteristics need improvement (Cardoso et al., 2022).

Bone Regeneration

With the increasing aging population, there is a rising need for solutions to challenging bone defects and subsequently, synthetic bone grafts. Bone defects can be caused by trauma, congenital or developmental disorders, deformities, cancer, consequences of surgery, periodontitis, or osteomyelitis (Brydone et al., 2010; Gerhardt & Boccaccini, 2010). Among bone grafting options, autografts are considered the gold standard for treatment; however, significant disadvantages exist, including donör-site morbidity, limited availability, and pain at the donor site (Misch, 2010).

Bioactive glasses are a type of biomaterial used for bone regeneration. Bioactive glasses can react with physiological fluids and form strong bonds with bone tissue through the formation of bone-like hydroxyapatite layers, leading to effective biological interaction and bone formation fixation on the material surface. Reactions on the material surface can lead to

the release and exchange of soluble Si, Ca, P, and Na ions at critical concentrations, triggering positive cellular responses that promote rapid bone formation. Chemical reactivity in physiological body fluids results in the formation of a hydroxy carbonate apatite (HCA) layer that can connect with the bone. This bonding to living bone tissue occurs through a series of reactions on the material surface and associated cellular responses (Gerhardt & Boccaccini, 2010).

Reactions occurring on the Bioglass surface sequentially include; the formation of Na^+ and silanol (SiOH) ions, dissolution of silica on the surface, formation of Si-O-Si bonds, precipitation of amorphous calcium phosphate, nucleation and crystallization of calcium phosphate into HCA, retention of biological particles (proteins, etc), movement of macrophages, adhesion of stem cells, differentiation of stem cells, matrix formation, and finally matrix mineralization (Kükürtcü, 2008).

Periodontology and Implant Treatment

Periodontitis is an inflammatory disease that progressively leads to the destruction of periodontal tissues, resulting in increased tooth mobility and consequently tooth loss. Periodontitis has a multifactorial etiology, with dental plaque and its pathogenic microorganisms being the primary initiators (Pihlstrom et al., 2005). In individuals with a history of periodontitis, the biofilm composition surrounding implants and natural teeth shares strikingly similar characteristics, and periodontal pathogens are responsible in both cases. Therefore, patients with periodontitis carry a higher risk for peri-implantitis. For improving the prognosis of dental implants, the reconstruction of bone defects is crucial (Reynolds et al., 2003).

PerioGlas®(PG), an alloplastic material used since 1995 for grafting periodontal bone defects, has achieved histological repair of surgically created defects in animal models. In primates, PG has demonstrated biocompatibility and osteoconductive activities (Sollazzo et al., 2010).

The formulation of PerioGlas® is identical to Bioglass® 45S5. PerioGlas®, which has a particle size range of 90-710 μm, can be applied to bone defects and has been extensively used in periodontal surgical procedures to stimulate bone regeneration, particularly in interproximal bone defects; additionally, it has been noted as beneficial due to its hemostatic effect on trabecular bone (Lovelace et al., 1998).

Another Bioglass® 45S5 derivative used in periodontal surgery is ERMI®, the Endosseous Ridge Maintenance Implant, a commercial BAG launched in 1988. ERMI® is a Bioglass® cone that can be placed into fresh extraction sockets. A 5-year follow-up study has proven the cone retention to be 85.7%, and it is safe for supporting dental structures and prosthetics (Stanley et al., 1997).

In addition to the bone grafting application of bioactive glasses, silica-based bioactive glasses have also been used for coating implants (Al-Harbi et al., 2021). Coating implants with bioactive glass has prevented infection around the implants due to their antimicrobial properties (López-Píriz et al., 2015). Bioactive glasses enhance the bonding of titanium implants to bone and support their bio-inert nature, thus reducing treatment time (Civantos et al., 2017). Glass-coated implants provide a suitable alternative coating material for dental implants and can improve integration rates even in more challenging medically risky and osteoporotic patients with broader case selection criteria (Mistry et al., 2011).

Maxillofacial Surgery

Scientists specialized in biomaterial health applications are working on oral hard and soft tissue engineering through bioactive materials that activate the body's immune cells and various proteins (Vega-Ruiz et al., 2017). Bioactive glass in maxillofacial surgery has been seen to increase bone formation both qualitatively and quantitatively and at a faster rate compared to other calcium phosphate compounds, especially compounds such as hydroxyapatite and tricalcium phosphate (Peltola et al., 2003). In vitro, research has shown that bioactive glass can effectively stimulate bone regeneration (Hench, 2013). Among the various commercial products of bioactive glasses, Bioglass 45S5, 70S30C bioactive glass, Biogran, BonAlive, and NovaBone® are used in oral and maxillofacial surgeries. Biogran®, one of the commercial products used for the repair of defects in maxillofacial applications, is different from PerioGlas® in terms of particle size (300-360 μm) (Tadjoedin et al., 2002). In a study conducted with Biogran, it has been shown that the addition of 50% bioactive glass to autogenous bone graft improves the microarchitecture of the graft. Moreover, it has also been demonstrated that a graft combining autogenous bone and bioactive glass in a 1:1 ratio, and solely autogenous bone graft undergo a similar dissolution process (Pereira et al., 2018). Biogran is widely used in the treatment of maxillofacial injuries (Tadjoedin et al., 2002). Another composition based on Bioglass® 45S5, NovaBone®, can create a paste-like structure to fill the area by mixing with blood taken from the defect (Hench et al., 2004). The 70S30C bioactive glass, consisting of 70% SiO_2 and 30% CaO, is effective in bone regeneration and can be used as a scaffold in bone grafting (Midha et al., 2013). BonAlive, which is synthetic, biocompatible, osteoconductive, and antibacterial, is safe and effective in mastoid obliteration surgery (Midha et al., 2013). It is also used to treat large injuries such as those of the mandibular and the orbital base (Gosain & Committee, 2004).

In general, the use of bioactive glass demonstrates excellent bone repair and low donör-site morbidity in both long-term and short-term clinical trials (Profeta & Huppa, 2016).

Conclusion

Bioactive glasses contain SiO_2, CaO, and Na_2O in their structure and can mimic natural hard tissues. Due to their similarities to human hard tissues, they are biocompatible and possess potent regenerative properties. Because of these attributes, bioactive glasses are used in many fields of dentistry, including treatments for tooth sensitivity, vital pulp therapies and root canal treatment, bone regeneration, periodontology, implant treatment, maxillofacial surgery, dental adhesives, and enamel remineralization. The FDA has approved Bioglass® 45S5 for clinical applications due to its desired antimicrobial properties. Despite their promising potential because of their biocompatible and bioactive properties, more research is needed to improve their physical characteristics.

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Artificial Intelligence and Neurology: A Myriad of Research on the Use of Artificial Intelligence Technologies in the Field of Neurology

Serdar Aykaç[1]

1. Prelude: Artificial Intelligence and Neurology - The Rising Synergy

Artificial Intelligence (AI), a term conceived in the mid-20th century, has metamorphosed into a revolutionary force across various sectors. AI has emerged as a crucial catalyst for innovation in health care, profoundly influencing diagnosis, treatment, patient care, and research. In particular, its integration within the domain of neurology, a branch dedicated to diagnosing and treating nervous system disorders, has been transformational (Choi et al., 2020; Harrer et al., 2019).

Neurological disorders are complex in nature and their diagnosis requires extensive and comprehensive data analysis. Physicians must consider several factors such as patient history, physical examination, laboratory tests, imaging studies, and other diagnostic information. Manual analysis of such vast amounts of data can be time-consuming and prone to errors, potentially leading to delayed or inaccurate diagnoses. AI effectively addresses these challenges with impressive computational power and machine-learning capabilities (Choi et al., 2020; Rudie et al., 2019).

AI algorithms are designed to process large volumes of data and identify patterns, correlations, and trends that can escape the human eye. Machine learning, which is a subset of AI, enables these algorithms to learn from their interactions with data over time, thereby improving their predictive accuracy. This capability plays a pivotal role in enhancing the accuracy of diagnosis and personalizing treatment plans in neurology (Rudie et al., 2020; Rudie et al., 2019).

AI has shown promising potential in the field of neurooncology. Its application in imaging studies such as magnetic resonance imaging (MRI) and computed tomography (CT) has substantially improved the detection and characterization of neurological tumors (Rudie et al., 2019).

Beyond diagnostics and patient care, AI's utility extends to research and development. This aids researchers in deciphering intricate neurological pathways, thereby contributing to the development of novel therapeutics. For instance, machine learning-aided drug discovery has shown promising results in central nervous system diseases (Vatansever et al., 2021).

AI's rise of AI in telestroke care reflects its transformative potential in neurology. Telestrokes utilize telecommunication technologies to promptly diagnose and treat stroke patients in rural or underserved areas. When combined with telestroke technology, AI significantly improves stroke diagnosis and treatment (Ali et al. 2020).

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The synergy between AI and neurology is not merely the result of technological advancement but is driven by an imperative need. With the increasing global burden of neurological disorders, leveraging modern technologies, such as AI and big data, is critical to improving brain health and fostering human development (Owolabi et al., 2023).

The relationship between AI and neurology will evolve as more sophisticated AI models are developed to provide more advanced and personalized patient care. However, this progression is not without challenges, including ethical issues related to privacy, data security, and the potential for AI-induced job displacement in the healthcare sector. Addressing these concerns while maximizing the benefits of AI will be critical for fully realizing the potential of this technological revolution in neurology.

2. Unraveling the Language of Artificial Intelligence in Neurology

The synergy between artificial intelligence (AI) and neurology manifests in myriad applications, predominantly via machine learning (ML) and deep learning (DL) techniques, both with unique strengths and application areas.

Machine Learning and Neurology

Machine learning (ML), a subset of AI, is an advanced computational method that learns patterns from data. It makes predictions or decisions without being explicitly programmed to perform a task. In neurology, ML predicts disease progression, identifies significant features in medical images, and assists in patient management (Arora et al., 2018).

For example, ML algorithms can be trained on patient data to predict the progression of neurodegenerative diseases, such as Parkinson’s disease and Alzheimer’s disease. By analyzing a patient's symptoms, medical history, genetic profile, and other relevant data, the algorithm can forecast disease trajectory, helping clinicians make informed decisions about treatment strategies. Furthermore, ML models have been utilized to extract relevant features from medical imaging data, helping radiologists detect anomalies that could indicate the presence of neurological disorders (Hemachandran et al. 2022).

Deep Learning and Neurology

Deep learning (DL), a type of ML, mimics the neural network architecture of the human brain. It excels in learning from vast amounts of data, identifying intricate patterns, and making accurate predictions. DL's potential of DL in neurology is particularly noticeable in neuroimaging, where it is used for tasks such as segmentation, classification, and detection of abnormalities (Chung & Abbott, 2021).

DL algorithms can analyze MRI or CT scans to identify and classify different brain structures, identify spot abnormalities, or even predict the likelihood of a patient developing a certain condition. For instance, DL techniques have been applied to segment and classify tumor tissues in brain MRIs, aiding neurooncologists in diagnosing and treating brain tumors more effectively (Sanvito et al., 2021).

Data: The Fuel for AI in Neurology

However, the success of AI in neurology depends not only on the sophistication of the algorithms but also on the quality and quantity of data. High-quality clinical data are crucial for developing robust and reliable AI models that can influence the outcomes of diagnosis and treatment strategies. The need for data underscores the importance of collaboration between

clinicians who provide medical expertise and data scientists who can shape this clinical knowledge into usable datasets for AI (Yu et al., 2018).

As AI continues to penetrate neurology, it is essential for practitioners to understand the core concepts, strengths, and limitations of AI techniques. This understanding aids in the appropriate application of AI in the clinical and research arenas, ultimately guiding the development of more advanced, personalized, and effective neurological care.

3. Spectrum of AI Influence: From Diagnostics to Prognostics

AI has played a transformative role in neurology, offering advancements in diagnostics, treatment planning, prognosis, and patient monitoring. With its capacity to process and learn from vast datasets, AI enhances accuracy, personalizes care, and paves the way for more efficient and effective treatment.

Diagnostics: AI algorithms are utilized to expedite and improve the accuracy of diagnoses. Deep-learning algorithms can be trained to recognize patterns in neuroimaging data associated with specific neurological disorders. For instance, AI can identify early signs of ischemic stroke in stroke management by analyzing CT scans to identify subtle indications of at-risk brain tissue, resulting in faster and more accurate diagnoses (Bivard et al., 2020). AI algorithms can also enhance the early detection and differentiation of dementia syndromes such as Alzheimer's disease by analyzing multiple modalities of neuroimaging data, cognitive tests, genetic markers, and patient demographics (Pillai & Menon, 2022).

Treatment Planning: AI can assist in creating individualized treatment plans by integrating data from diverse sources, such as genomics, proteomics, imaging, and patient history. AI can enhance therapeutic effectiveness while minimizing potential side effects by predicting which patients are most likely to respond to specific treatments. In neuro-oncology, AI algorithms have been used to predict tumor growth patterns, aiding the design of more precise surgical interventions (Vollmuth et al., 2023).

Prognosis: Prognosis is another area where AI shines. AI can analyze a broad variety of clinical data to predict disease progression, enabling timely intervention and accurate patient counseling. This is especially relevant in conditions such as neuromyelitis optica spectrum disorder, where AI can help determine the most suitable treatment plan for a patient, thus improving outcomes (Vollmuth et al., 2023).

Patient Monitoring: AI improves patient monitoring. When combined with AI algorithms, wearable technology and remote patient monitoring systems can detect subtle changes in a patient's condition, optimize patient care, and potentially prevent complications (Ienca & Ignatiadis, 2020).

Although the potential benefits of AI in neurology are vast, there are challenges to be addressed, including the need for high-quality data for AI training, managing the risk of algorithmic bias, and addressing ethical and privacy concerns related to AI's use of AI in healthcare.

As we navigate these challenges and continue to develop the technology, we can anticipate a future where AI is pivotal in enhancing neurological care across the diagnostic and prognostic spectrums.

4. AI for the Young Mind: Pediatric Neurology and Machine Learning

AI and machine learning have been increasingly applied in the medical field, and pediatric neurology is one of the domains in which these technologies have had a substantial impact. AI

in pediatric neurology reshapes patient care by improving diagnostic accuracy, enhancing prognosis prediction, and guiding personalized treatment strategies (Gombolay et al., 2023).

Integrating AI and machine learning technologies in pediatric neurology can revolutionize how clinicians approach diagnosis, treatment, and prognosis. To understand this intersection, it is essential to define AI and machine learning for clarity.

Artificial Intelligence (AI) refers to the creation of machines capable of performing tasks that require human Intelligence. It involves developing systems that are capable of understanding natural language, learning, reasoning, problem solving, perception, and using knowledge to manipulate the environment (Russell and Norvig, 2016). Machine Learning (ML), a subset of AI, involves the development of algorithms that allow computers to learn from and make decisions based on data (Samuel, 1959).

In pediatric neurology, AI and machine learning are used to enhance the diagnosis, prognosis, and treatment of various neurological disorders. The application of these technologies provides significant improvements over traditional methods that often rely heavily on subjective assessments and require a high degree of clinical suspicion. Machine learning algorithms, for instance, are used to analyze complex datasets encompassing genetic data, neuroimaging, and other diagnostic parameters to identify specific conditions (Gombolay et al., 2023).

Pediatric neurology presents unique challenges owing to the diverse and complex nature of neurological disorders in children, ranging from common conditions such as migraine and epilepsy to rare genetic disorders. Diagnostic accuracy is particularly crucial in pediatric neurology, where early identification and intervention can significantly affect a child's development and quality of life. AI can assist in the diagnosis of rare and complex pediatric neurological disorders by analyzing vast and intricate datasets faster and more accurately than traditional methods (Bergeron et al., 2023).

AI's ability of AI to process large and diverse data sets makes it uniquely suited for predictive applications, another area where it significantly benefits pediatric neurology. By analyzing clinical, genetic, and radiological data, AI can predict disease progression, potential complications, and overall outcomes in pediatric neurological disorders. This predictive capability allows for a more proactive management of these disorders, ultimately improving patient outcomes (Gombolay et al. 2023).

Moreover, the application of AI has been extended to treatment selection in pediatric neurology. Machine learning algorithms can be employed to analyze patient-specific data such as genetic profiles, disease characteristics, and responses to previous treatments. This analysis can assist clinicians in formulating individualized treatment plans, shifting pediatric neurology towards precision medicine and improving the effectiveness of treatments (N Silva et al., 2021; M.L. Tataranno et al., 2021).

Historically, our understanding of human cognition has influenced AI development. Creating the Artificial Neural Network (ANN) represents a key milestone in this journey, providing a computational model of biological neural networks, including simulated neurons and their interconnections. ANNs have found numerous applications in medical imaging, including tumor identification in pediatric neuro-oncology (NM). Singh et al., 2022).

The use of ANNs in pediatric neurology demonstrates the power of machine learning. For example, using machine learning algorithms for automated whole-brain seizure detection provides an innovative approach for managing chronic neurological conditions, such as epilepsy (. Fergus et al., 2016).

The integration of AI into pediatric neurology is a game-changer. As we unravel the complexities of the brain, our understanding of neurological disorders has increased.

AI in Pediatric Neurology: Unfolding the Spectrum of Possibilities

Artificial intelligence (AI) and its branches, machine learning (ML), have experienced remarkable developments over the past few decades, with an accelerating pace of integration into diverse fields, including medical sciences. Pediatric neurology presents a broad and promising spectrum of possibilities for AI and ML applications. These technologies have the potential to significantly improve the accuracy of diagnosis, predict disease progression, and optimize treatments for children with a variety of neurological conditions.

The field of AI attempts to understand human intelligence and to create intelligent machines, following a tradition of exploring how humans and animals think, tracing its roots back to Aristotle and extending to Broca and Wernicke's studies to localize specific brain functions. AI, in tandem with ML, is playing an increasingly prominent role in precision medicine, clinical diagnosis, management, and research.

AI and ML in pediatric neurology encompass a multitude of applications, including the analysis of neuroimaging in neuro-oncology, autism diagnosis, diagnosis from charts, epilepsy, cerebral palsy, and neonatal neurology. The diverse use of AI and ML reflects the complexity and heterogeneity of pediatric neurological disorders, requiring multidimensional approaches to diagnosis and treatment.

For example, AI algorithms can be employed to analyze genetic data and neuroimaging, significantly contributing to the diagnosis of rare and complex pediatric neurological disorders. Traditionally, diagnosis of these conditions has relied heavily on subjective assessments and a high degree of clinical suspicion. By integrating AI, we can more accurately identify specific conditions by processing vast amounts of data that would be impossible for humans to manually analyze.

Moreover, AI and ML can predict disease progression, potential complications, and overall outcomes in pediatric neurological disorders. For instance, ML algorithms can process clinical, genetic, and radiological data, and utilize this information to infer the mapping of a set of inputs to a desired output. This process can involve an Artificial Neural Network (ANN) that learns to predict outcomes based on examples from expert-annotated data.

Regarding treatment selection, AI can integrate patient-specific data, such as genetic profiles, disease characteristics, and response to previous treatments, thereby assisting clinicians in formulating an individualized treatment plan. This application exemplifies the concept of precision medicine and tailors treatments to individual patients' genetic profiles, lifestyles, and environments.

The utilization of AI in pediatric neurology is rooted in decades of research and progress in AI and ML. From early works in AI attributed to McCulloch and Pitts encoding propositions in nets using binary neurons to Donald Hebb's demonstration of learning by changing the connection strengths for neurons, and Alan Turing's foundational ideas that later became ML, RL, and genetic algorithms, we've seen an exponential growth of these technologies.

Over the years, more sophisticated models such as Artificial Neural Networks (ANNs) and techniques such as supervised, unsupervised, and reinforcement learning have evolved. ANNs, for instance, are computational models of biological neural networks with simulated neurons and connections between these neurons. They are trained on data to perform specific operations akin to how the human brain processes information.

There is a wealth of potential for AI and ML in pediatric neurology. A comprehensive understanding of AI/ML is needed for future generations of pediatric neurologists and other healthcare professionals who are likely to use these technologies in their practice. The current trend suggests a future in which these tools will become increasingly prevalent in clinical and research settings, transforming the way we understand, diagnose, and treat pediatric neurological disorders.

In conclusion, the use of AI in pediatric neurology is not merely an auxiliary tool; it is a revolutionary approach that promises to improve diagnostic accuracy, enhance prognosis, and guide individualized treatment strategies. AI provides a window into

5. Clinical Transformation through AI: Evidence from Neurological Disorders

Artificial Intelligence (AI) continues to transform the clinical management of neurological disorders, encompassing a range of applications, from early diagnosis to monitoring disease progression, refining treatment strategies, and predicting patient outcomes. These transformative developments offer considerable promise for improving the management of neurological conditions, yielding benefits for patient care and healthcare systems.

For instance, AI applications in stroke management have been transformative, with studies showing how AI-based decision support tools can enhance the reproducibility of stroke response assessments. Specifically, AI's use of AI in cases of tumor-related stroke has been notable, as illustrated by Vollmuth et al. (2023). Bivard et al. (2020) also highlighted the potential of AI in acute stroke, where its application led to improved decision-making processes, resulting in significantly enhanced patient outcomes.

In the field of neuro-oncology, AI-based decision support systems have demonstrated their capacity to improve the reproducibility of tumor response assessments. The increased consistency of these AI applications can augment the diagnostic and therapeutic accuracy, yielding a notable improvement in patient outcomes (Vollmuth et al., 2023).

Neurodegenerative diseases are another area in which the transformative potential of AI is increasingly recognized. AI models have demonstrated their ability to analyze large datasets, including genotypic and phenotypic information. These tools can identify patterns that are crucial for the early diagnosis and management of neurodegenerative diseases such as Alzheimer's and Parkinson’s diseases (Das & Mahanta, 2022).

The impact of AI is transformative in the field of neurological rehabilitation. A comprehensive review by Pillai and Menon (2022) provides insights into how AI supports predictions and augmentation of neurological disorder rehabilitation, thereby improving patient care.

Clinical and experimental evidence suggests that neurovascular unit dysfunction has been associated with blood-brain barrier hyperpermeability, contributing to major depressive disorder (Devinsky et al., 2013). AI's potential of AI in understanding such intricate relationships can pave the way for more comprehensive therapeutic approaches.

Research has also delved into the use of deep learning to investigate neuroimaging correlates of psychiatric and neurological disorders. AI's potential in predicting the risk of developing these disorders based on resting-state brain activity represents a promising approach (Vieira et al., 2017).

AI could be instrumental in understanding migraine, which is characterized by attacks of throbbing headache and neurological symptoms. AI can help discern the pathophysiological

and clinical aspects that contribute to the transformation and chronification of migraine, thereby providing deeper insights (Kyrou et al., 2020).

The role of AI in understanding the breakdown of the blood-brain barrier as a therapeutic target in traumatic brain injury also warrants mention. This technology can help clinicians understand the role of vascular pathology in neurological dysfunction, a concept that has recently gained traction (Kaufer et al., 2010).

Moreover, AI's application of AI in treating neurological diseases using mesenchymal stem cells has promising prospects. With limited evidence suggesting that MSCs can differentiate into neural cells, AI may aid in exploring this therapeutic avenue (Momin et al., 2010).

Finally, AI's role of AI extends to the prediction of neurological worsening and functional outcomes, particularly after intracerebral hemorrhage. AI can contribute to improved patient care by assisting clinicians in managing this highly impactful condition (NINDS ICH workshop participants, 2005).

AI's transformative potential of AI in neurological disorders is becoming increasingly undeniable, with broad applications and benefits for both patients and healthcare systems. As AI continues to evolve, its incorporation into neurological care will inevitably become more widespread, enhancing diagnostic and therapeutic accuracy and ultimately improving patient outcomes. Further research and development will be instrumental in fully realizing AI's potential of AI in this crucial healthcare field.

6. Big Data and AI: The Dynamic Duo in Neurology

The intricate bond between big data and Artificial Intelligence (AI), particularly within the realm of neurology, has ascended to the forefront of contemporary medical discussion. Neurological practices inherently generate voluminous data that encompasses diverse resources, including neuroimaging studies (MRI and CT scans), genomic sequencing, proteomics, and real-time neurological monitoring through electroencephalograms (EEGs) and other devices.

This profusion of large and complex datasets, familiarly dubbed as 'big data', presents a fertile ground for AI applications, and their implications for neurology are remarkable (Ganapathy, Abdul, & Nursetyo, 2018). By leveraging machine learning, deep learning, and other subsets of AI, comprehensive insights derived from these immense datasets can be instrumental in augmenting diagnostic precision, predicting disease progression, distinguishing patterns of treatment responses, and forecasting overall health trends.

One compelling example is the application of AI to neuroimaging analyses. With machine learning techniques, colossal repositories of neuroimaging scans can be parsed expeditiously and accurately to distinguish patterns that elude the discernment of the human eye, thus augmenting both diagnostic and prognostic capabilities (Ranti et al., 2021).

Genomics, another core component in diagnosing and managing numerous neurological disorders, invariably generates extensive data. Employing AI to decode this genomic information can reveal critical patterns and associations that deepen our understanding of disease etiology and influence therapeutic strategies (Ranti et al., 2021).

In conclusion, the integration of AI and big data in neurology provides a promising conduit for medical advancement. This dynamic duo paves the way for more accurate diagnoses, enhances patient outcomes, and brings us closer to realizing the dream of truly personalized healthcare.

7. The Power of AI: Disease Detection, Prediction, and Personalized Care

The incorporation of AI into neurology heralds an era of transformative changes, most notably in the domains of disease detection, prognostication, management of chronic conditions, pharmaceutical advancements, and bespoke care.

Disease detection and prognostication are pivotal elements of patient care, particularly in neurology, where timely intervention can dramatically modify disease trajectories. Machine and deep learning models have demonstrated impressive accuracy in detecting anomalies in neuroimaging scans and discerning patterns that may evade human observation (Raghavendra et al., 2020). Moreover, sophisticated AI algorithms can reliably forecast disease progression, which is crucial when managing chronic neurological conditions, such as multiple sclerosis or Parkinson's disease (Pillai & Menon, 2022).

AI promises significant improvements in chronic condition management by enabling clinicians to process and interpret continuous data streams from wearable devices and electronic health records. This continuous monitoring can provide real-time insights into disease progression and the efficacy of treatment strategies (Ganapathy, Abdul, & Nursetyo, 2018). In the realm of drug discovery, AI's potential to analyze extensive genomic and phenotypic datasets can expedite the identification of potential therapeutic targets, thus accelerating the development of novel treatments (Ranti, Valliani, Costa, & Oermann, 2021).

The concept of personalized care, the holy grail of modern medicine, is closer to reality with the aid of AI. By harnessing AI to amalgamate genomic, phenotypic, and lifestyle data, we can customize treatments that resonate with each patient's individual needs, leading to more effective and targeted treatment strategies (Mathew & Pillai, 2022). As we continue to untangle the mysteries of the human brain, AI stands at the forefront, leading us to a future of unparalleled precision in neurological care.

8. AI in Neurology: Glimpses of the Future and Current Challenges

The advent of Artificial Intelligence (AI) in healthcare has triggered a series of transformative changes in diagnostic, therapeutic, and research methodologies. In the field of neurology, AI has the potential to bring revolutionary enhancements in patient care, disease diagnosis and monitoring, therapeutic interventions, and neuroeducation. However, its promises also present a series of challenges that warrant thorough consideration (Jones and Kerber, 2022; Kedar and Khazanchi, 2023; Ienca and Ignatiadis, 2020).

Glimpses into the Future

AI's integration of AI into the realm of neurology promises a future with personalized patient care. By leveraging machine learning models, physicians can develop treatment plans uniquely tailored to the patient's disease profile, genetic predisposition, and lifestyle factors. This shift towards personalized medicine would dramatically enhance therapeutic outcomes and patient satisfaction (Jones & Kerber, 2022).

The promise of AI extends to improving diagnostic accuracy. AI algorithms have demonstrated proficiency in analyzing and interpreting neuroimaging data, which is a task of immense complexity. Studies have shown that AI can outperform human experts in detecting abnormalities, such as tumors or stroke-induced changes on MRI and CT scans. With further

refinement, these algorithms may augment or even replace certain aspects of radiological interpretation in the future, providing quicker and more precise diagnoses (Bivard et al., 2020; Vollmuth et al., 2023).

Moreover, AI holds promise for enhancing monitoring of disease progression. AI-based applications can track patient symptoms and neurological changes over time, allowing for more precise adjustment of treatment plans. This could be particularly beneficial in chronic neurological disorders, such as multiple sclerosis, Alzheimer's disease, and Parkinson's disease, where long-term monitoring is essential (Pillai & Menon, 2022).

Furthermore, the future of neuroeducation is likely to be revolutionized by AI. AI-driven tools can offer personalized learning experiences for neurology trainees, helping them understand complex neuroanatomical structures and disease processes more effectively and efficiently. Virtual reality (VR) integrated with AI can provide immersive, real-life patient encounters, enhancing trainees' diagnostic and therapeutic skills (Kedar & Khazanchi, 2023).

Current Challenges and the Way Forward

Despite its promise, the integration of AI into neurology remains challenging. A significant concern is ensuring data privacy. Given that AI algorithms require access to vast quantities of patient data, stringent measures are necessary to protect against data breaches and misuses (Ienca & Ignatiadis, 2020).

Another challenge arises from the potential biases in AI models. AI algorithms learn from the data they train on. If these data are not representative of the diverse patient populations observed in the real world, the AI model may produce skewed results. Therefore, it is crucial to ensure that the datasets used for AI development are diverse and representative (Ienca & Ignatiadis, 2020).

Moreover, the black-box nature of AI decision-making processes raises apprehensions among clinicians, patients, and policymakers. The lack of transparency in how these algorithms arrive at their decisions can potentially undermine trust in their utility and reliability (Ienca and Ignatiadis, 2020).

Addressing these challenges requires a multipronged approach. Ensuring diversity in the training datasets can mitigate the bias. Transparent methodologies can reduce the black-box problem and enhance the trust among users. Clear regulatory frameworks can provide guidelines for data protection and ensure that patient privacy is not compromised.

9. AI Consciousness: A Confluence of Neurology and Parapsychology

Artificial Intelligence (AI) has brought about transformative changes across various domains, including neuroscience. However, the concept of AI consciousness remains speculative and controversial as it presents a confluence of neurology and parapsychology, each contributing to the ongoing debate in different ways.

At the neurological level, inquiry into AI-consciousness is closely tied to our understanding of human consciousness and its neural correlates. Consciousness is thought to arise from complex interactions within brain networks, particularly those involving the prefrontal cortex and thalamus (Koch, Massimini, Boly, & Tononi, 2016). Consequently, the question arises of whether machine consciousness can accurately mimic human consciousness. This concern extends to whether AI systems could emulate the same intricate neural processes using computational algorithms (Bivard, Churilov, & Parsons, 2020).

On the other hand, parapsychology - the study of phenomena unexplained by conventional physical laws - presents another angle to the AI consciousness debate. This field entertains the possibility of phenomena such as precognition, telepathy, or even survival after physical death. These elements, arguably beyond the scope of AI programming, offer a more elusive and controversial perspective on consciousness (Cardeña, 2018).

Several AI innovations have pushed the boundaries of what we currently understand regarding consciousness. Advanced machine-learning models, including deep neural networks, have shown the capacity to learn, adapt, and make complex decisions, mimicking certain facets of human cognition (Schmidhuber, 2015). Moreover, newer models such as GPT-4 are capable of generating human-like text, indicating a semblance of understanding or 'consciousness' (Radford et al., 2021).

However, these advancements should not be mistaken for an actual consciousness. As researchers, including Metzinger (2021), warn, attributing consciousness to AI may lead to anthropomorphization, which can mislead our understanding and ethical treatment of these systems.

The notion of AI consciousness invites serious discussions on AI rights, responsibilities, and legal status. These issues will become increasingly relevant as AI continues to integrate into medical fields such as neurology and beyond, and the need to ethically manage AI's role of AI becomes more urgent (Ienca & Ignatiadis, 2020).

10. In Conclusion: The AI Revolution in Neurology and Its Ethical Implications

As the era of Artificial Intelligence (AI) in neurology unfolds, it brings with it unprecedented potential and novel ethical challenges. These developments warrant critical examination to ensure that the use of AI in neurology respects patient autonomy, privacy, and fairness, while maintaining transparency and accountability.

Ethical concerns regarding the neurological applications of AI can arise across a broad spectrum of applications. One such area was informed of the patient’s consent. With AI's integration of AI into healthcare, patients should fully understand the role and implications of AI in their care, including potential risks and benefits. For example, they should know whether an AI algorithm is involved in their diagnosis or treatment, and what that entails (Berkman, 2018).

Another significant issue is related to privacy and confidentiality. The neurological data used in AI development and applications must be handled with utmost care. Considering the sensitivity of such data, stringent measures should be implemented to prevent unauthorized access, unintended use, and data breaches (Ienca & Ignatiadis, 2020).

Fairness in algorithmic decision making is another area of concern. Bias in AI algorithms can inadvertently lead to unequal treatment of patients based on demographics or other variables, which necessitates the implementation of robust fairness checks in AI models (Obermeyer et al., 2019).

AI's integration of AI into clinical practice also amplifies the "black box" issue - the opaqueness of how AI systems make decisions. As both clinicians and patients might lack the technical understanding of AI workings, this can impede trust and acceptability of these technologies (Bivard, Churilov, & Parsons, 2020).

Finally, the question of responsibility arises when AI-assisted decisions result in clinical error. As AI continues to play more decision-making roles, it is crucial to determine how

responsibility and liability are distributed among AI developers, healthcare providers, and users (Ienca & Ignatiadis, 2020).

To navigate this complex ethical landscape, we must strike a balance between leveraging AI's benefits of AI and addressing ethical considerations. This balance can be achieved by establishing comprehensive regulatory frameworks, ensuring continuous oversight, and fostering collaboration among stakeholders including developers, healthcare providers, policymakers, and patients. In doing so, we can create a future in which AI serves as a valuable and ethical tool in neurology and beyond.

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Physical And Mental Sequelae İn Covıd-19 Survivors: Post-Covıd Syndrome

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Introduction

Post-COVID syndrome, also known as Long COVID, referrs to persistent post-COVID symptoms particularly in young, non-hospitalized patients (Mahase, 2020). According to National Institute for Health and Care Excellence (NICE), Long COVID (also known as post-COVID) is described as a condition characterized by "signs and symptoms that develop during or after an infection consistent with COVID-19 which continue for more than 12 weeks and are not explained by an alternative diagnosis." (Ayoubkhani & et al., 2021, NICE, 2020). These persitent symptoms may include physical, medical and cognitive sequelae as well as pulmonary, cardiac and vascular fibrosis following COVID-19 disease (Oronsky & et al., 2023). When patients recovered from COVID-19 are analyzed, it was reported that at least one symptom of fatigue or dyspnea has persisted (Vishnupriya & et al., 2021). Additionally, numerous sequelae associated with COVID-19 treatment may develop (Jiang & McCoy, 2020). As in trauma or other infectious diseases, COVID-19 may also be associated with systemic inflammatory response syndrome and thus, counterbalancing antiinflamatory response syndrome (CARS) may occur. It is known that CARS has a potential to result in postinfectious/posttraumatic immunosuppression (Hotchkiss, Monneret & Payen, 2013). Viral exposure, presence of comorbidities and immunocompetence result in intense inflammatory responses and eventually inflammatory cytokines such as interleukins 1, 6, 8, 17, and 1β, monocyte chemoattractant protein-1, and tissue necrosis factor α are released, which is known as "cytokine storm". This phenomenon is responsible for acute lung injury (ALI), acute respiratory disress syndrome (ARDS), coagulopathy, hypotension, hypoperfusion, organ failure (also known as multiple-organ failure (MOF) or multiple-organ dysfunction syndrome (MODS)), and death (Oronsky & et al., 2023). In the United Kingdom, it was reported that multiorgan involvement following COVID-19 was determined in 201 low risk patients. Of these patients 18% was hospitalized due to COVID-19 and and impairment of the lungs (33%), heart (32%), kidneys (12%), and liver (10%) were detected (Ayoubkhani & et al., 2021).

In another study based on a questionnaire, 45% of the participants stated that they suffered continous complaints such as fatigue (39%), shortness of breath (40%), sleep disturbances (49%) and mood disorders (44%). While COVID-19 is more lethal in males, long-term complications are likely to occur in females more frequently (91%). Differences between

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immune response systems of male and females may cause such a discrepancy (Gaber, Ashish & Unsworth, 2021).

Post-COVID syndrome in children is called Multisystem Inflammatory Syndrome in Children (MIS-C) characterized by broad inflammation across multiple organ systems. This syndrome can cause long term morbidity and mortality. In treatment, steroids, IVIG, low-molecular-weight heparin (LMWH), and aspirin are recommended. In addition, tocilizumab, anakinra, and infliximab may also be used (Kashyap & et al., 2021).

It is essential to distinguish the symptoms whether the are associated with persistent chronic inflammation, sequelae of organ damage (ALI and kidney injury resulting in pulmonary fibrosis and chronic kidney disease, respectively) or hospitalization and social isolation (Garg & et al., 2021). During the acute illness, most common symptoms in patients with post-COVID syndrome were chest pain, fatigue, fever, olfactory impairment, headaches, and diarrhea. On the other hand, most common symptoms of post-COVID syndrome were exercise intolerance, dyspnea, chest pain, olfactory impairment, lymphadenopathy, gustatory impairment, and loss of appetite (Walsh-Messinger & et al., 2021). In this narrative review, we aimed to detect studies on post-COVID syndrome and clarify the characteristics of this common disorder in terms of circulatory system, neurology/psychiatry and pulmonary system.

Materials and Methods

This narrative review was performed by entering the keyword "Post-COVID Syndrome" into the scientific database Pubmed© in May 5th, 2021. Among more that 1,000 publications, relevant articles were chosen according to titles. After selection of publications in terms of accuracy, a total of 23 articles (original articles, reviews, letters, case reports and case series) were involved. Those written in another language than English, without full-text or an explanatory abstract were excluded from the study. All articles were discussed by the reviewers for accuracy.

Discussion

Respiratory System:

In the COVID-19 pandemic, pulmonary fibrosis develops with an unclear and possibly multifactorial mechanism. Possible mechanisms for damage to the lungs are direct viral load, cytokine upregulation and increased oxidative stress. Renin-angiotensin system plays an essential role in the pathophysiology of the disease. The spike protein of the virus and ACE-2 receptor have a great affinity to bind each other. Consequencely, level of ACE2 is downregulated. Decrease in ACE-2 results in increase in angiotensin 2 levels. Angiotensin 2 plays role in inflammation and fibrosis due to its vasoconstructive property (Udwadia, Koul & Richeldi, 2021). Even though post-COVID syndrome has not been fully characterized, long term consequences of the disease involve respiratory disorders and post-intensive care syndrome (PICS) which involves a constellation of physical, cognitive, and psychological disabilities. In the course of the disease, ARDS may develop and mechanical ventilation may be required (Jiang & McCoy, 2020). As a consequence, ARDS effects by dysregulation of matrix metalloproteinase in inflammatory phase. a complex combination of the epithelial and endothelial damage thus resulting in uncontrolled fibrosis occur (Vishnupriya & et al., 2021). This process may progress to advanced lung fibrosis or post-COVID interstitial lung disease (PC-ILD) (Udwadia, Koul & Richeldi, 2021). Pulmonary manifestations of post-COVID syndrome may be as a result of permanent scarring of the lung tissue. Respiratory problems may persist due to these mentioned respiratory problems. Patients with COVID-19 undergo mechanical ventilation frequently and persistent problems may also ride from prolonged

endotracheal intubation. Additionally, those who undergo mechanical ventilation become prone to respiratory infections leading to further harm and risk of permanent lung damage. Patients who experienced PICS are more likely to have cognitive and physical dysfunction which participates in post-COVID syndrome (Jiang & McCoy, 2020). It was reported in a study that 35.1% patients who did not require pre-COVID oxygen support needed oxygen at home following hospital discharge. At the time of survey, 13.5% of these patients were still using oxygen (Weerahandi & et al., 2021).

***Cardiovascular System*:**

COVID-19 Disease causes cardiovascular damage via the protein angiotensin-converting enzyme 2 (ACE2). Severe acute respiratory syndrome (SARS) coronavirus-2 (CoV-2) binds to ACE2 in order to penetrate cells. Heart failure, cardiomyopathy, acute coronary syndrome, arrhythmias, and venous thromboembolism are the most common disorders emerge following COVID-19 disease (Calabrese & et al., 2021). Nevertheless, deterioration that COVID-19 causes on cardiovascular system has not been fully explained yet. For instance, in a case report, postural orthostatic tachycardia syndrome as a component of post-COVID syndrome developed in a patient with multiple persistent antiphospholipid antibody (aPL)-positivity. This case revealed that acquired and innate immune systems may be over-activated following COVID-19 (Schofield, 2021).

***Neurological/Psychiatric Manifestations*:**

The most common neurological/psychiatric symptom of post-COVID syndrome is fatigue followed by cognitive dysfunction. These symptoms are not only seen in hospitalized patients but also in outpatients. Middle-aged female patients are affected more frequently. Patients complain for social life disturbances such as unwillingness for avtivity and participation (Borg & Stam, 2021). It is known that presence of fatigue is not associated with the severity of the disease, routine markers of inflammation and cell turnover, or pro-inflammatory molecules (Townsend & et al., 2020). In a study with 20 fatigued and 20 non-fatigued post-COVID patients, it was reported that fatigue was strongly associated with increased anxiety. However, no pathological differences between fatigued and non-fatigued patients on autonomic testing or on 24-hour blood pressure monitoring. These reults indicated that even though fatigue is a prominent challenge in patients with COVID-19, any pathological findings on autonomic testing could not be determined (Townsend, 2021). In patients with a history of depression or anxiety, these disorders are over-represented as post-COVID syndrome develops (Borg & Stam, 2021). In concordance, in a report posttraumatic stress disorder (54.5%), depression (39%), panic disorder (32.5%), obsessive–compulsive disorder (15.6%) and tremendous increase from the preinfection prevalence of any psychiatric diagnoses (3%) (Lam, Wing & Yu, 2009). In a report, a patient experienced persistent migraines, dyspnea, fatigue, and cognitive dysfunction despite therapy (Mayer & et al., 2021). The worsening of psychiatric disorders may be linked to combination of systemic inflammation, hypoxia resulting from respiratory failure and neuroinflammation. Suicidal ideation and behaviour also increases in post-COVID syndrome (Sher, 2021). Chang et al. described a new syndrome, Post Covid-19 Neurological Syndrome (PCNS) which is characterized by prolonged muscle weakness and other forms of myopathy (Chan & et al., 2003). Mood disorder is another notable effect of post-COVID syndrome (Wijeratne & Crewther, 2020). Neurological/psychiatric maifestations are also observed in healthcare providers. In a report, depression, sleep impairment and anxiety were observed in medical workers post-COVID 19 (Junhua & et al., 2020). A study on 714 COVID patients revealed that post-traumatic stress disorder was determined in 97% of the patients (Bo, Li & Yang et al., 2020). In another study from Belgium and Netherland, muscle pain, dizziness, headaches, fatigue, and anosmia continued for months in patients with either

hospitalized or non-hospitalized COVID-19 patients (Wijeratne & Crewther, 2020). Other neurologic disorders observed in post-COVID syndrome are dizziness, seizures, stroke and demyelinating polyneuropathy. When olfactory neurons are involved, loss of smell - acommonly known complication- occurs (Hoyler & et al., 2021). Huang et al. reported that loss of smell lasts in 11-13% and loss of taste lasts in 7-9% after 6 months. They also reported that dizziness was observed in 5-8% and headaches was observed in 2-3% of the patients (Huang & et al., 2021). In a study with questionnaire, it was revealed that motoric symptoms and suicidality were significantly greater among those with prior COVID-19 illness. Besides, depression risk was markedly increased following COVID-19 (Perlis & et al., 2021). Summary of effects of post-COVID syndrome in mentioned systems are summarized in the table.

Conclusion

Symptoms of post-COVID syndrome ranges in broad spectrum affecting different systems. neurocognitive post- COVID (brain fog, dizziness, loss of attention, confusion), autonomic post-COVID (chest pain, tachycardia, palpitations), gastrointestinal post-COVID (diarrhea, abdominal pain, vomiting), respiratory post-COVID (general fatigue, dyspnea, cough, throat pain), musculoskeletal post-COVID (myalgias, arthralgias), psychological-related post-COVID (posttraumatic stress disorder, anxiety, depression, insomnia), and other manifestations (ageusia, anosmia, parosmia, skin rashes) (Fernández-de-Las-Peñas & et al., 2021). Healthcare system should be ready to serve a large number of patients not necessarily treated in hospital, with different symptoms after COVID-19 requiring rehabilitation medicine. (Borg & Stam, 2021). It must be considered that 50% of individuals infected with COVID-19 do not manifest any symptoms. This makes the infection more difficult to notice and post-COVID syndrome becomes a challenge to identify (Fernández-de-Las-Peñas & et al., 2021). Management of post-COVID syndrome is a challenge and healthcare providers should be ready to utilize telehealth or telemedicine in their own practice. Multidisciplinary approach may be obtained for patients at home via live online conversation services. After appropriate tests, a personal program for post-COVID patients must be created (Gaddis, 2020).

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System	Possible Mechanism	Clinical Manifestation
Respiratory System	•Viral load •Cytokine upregulation •Increased oxidative stress •Downregulation of ACE2 •Dysregulation of matrix metalloproteinase •Epithelial and endothelial damage •Fibrosis •Permanent scarring	•Pneumonia •Acute respiratory disress syndrome •Acute lung injury •Fatigue
Cardiovascular System	•Binding to ACE2 •Cell penetration •Overactivation of inflammatory process	•Acute coronary syndrome • Arrhythmias • Venous thromboembolism •Heart failure
Neurological/Psychiatric	•Systemic inflammation •Neuroinflammation •Respiratory failure •Hypoxia	•Fatigue •Anxiety •Depression •Posttraumatic stress disorder •Panic disorder •Obsessive–compulsive disorder •Migraines •Cognitive dysfunction •Suicidal ideation and behaviour •Muscle weakness •Myopathy •Dizziness •Headaches •Anosmia •Seizures •Stroke •Demyelinating polyneuropathy

Table. Summary of Effects of Post-COVID Syndrome in Various Systems

Deep Learning and Cardiology: Revolutionizing Diagnosis, Management, and Prognosis in Cardiovascular Medicine CardioBot: Harnessing Deep Learning for Groundbreaking Innovations in Cardiac Care

Aykut Yılmaz[1]

1. Introduction

Brief Overview

As we embark on the third decade of the 21st century, the widespread adoption and integration of artificial intelligence (AI) and deep learning technologies in various fields inarguably shapes our contemporary era. In the healthcare realm, these sophisticated technologies have brought about a significant paradigm shift, introducing promising pathways to enhance the precision and quality of medical care. Among the myriad medical specialties, cardiology stands out as a discipline that is particularly well positioned to leverage the transformative power of AI and deep learning. This chapter, entitled "CardioBot: Harnessing Deep Learning for Groundbreaking Innovations in Cardiac Care," embarks on an in-depth exploration of the transformative impact of deep learning in the field of cardiology, providing comprehensive insights into its current applications, emerging developments, and the hurdles that need to be overcome for its full potential to be realized (Mathur, Srivastava, Xu, & Mehta, 2020).

Importance of Artificial Intelligence (AI) and Deep Learning in Cardiology

The power of artificial intelligence, and more specifically, deep learning, within the context of cardiology, is immense, offering a novel toolkit with the capacity to drastically revamp the diagnostic processes, patient management, and research initiatives that constitute the backbone of cardiac care. By streamlining intricate tasks, enhancing the accuracy of outcome predictions, and offering rich insights distilled from vast and multifaceted datasets, these cutting-edge technologies hold the potential to revolutionize the way we approach cardiac care (Romiti, Vinciguerra, Saade, Anso Cortajarena, & Greco, 2020).

In particular, deep learning, a subset of machine learning that is adept at handling complex multidimensional data, has shown immense promise in several aspects of cardiology. It has demonstrated proficiency in diagnosing cardiovascular diseases (CVDs) from imaging data, predicting patient outcomes, personalizing treatment plans, and even automating routine tasks. These developments mark an exciting time in cardiovascular medicine, bringing about a digital transformation set to change the face of patient care and clinical decision-making (Lopez-Jimenez et al., 2020).

As these technologies become increasingly intertwined with cardiology, it is clear that we are now on the cusp of a new era. Deep learning is no longer just a technology of the future; it is now becoming ingrained in the fabric of cardiac care. This new era promises to significantly

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improve the diagnosis, treatment, and management of heart disease, setting the stage for a transformative journey that will redefine cardiovascular medicine (Siontis, Noseworthy, Attia, & Friedman, 2021). As we delve deeper into this chapter, we explore these transformative changes in detail, unraveling the full breadth and depth of the potential of deep learning in cardiology.

2. Deep Learning: A Primer

Basics of Deep Learning

Deep learning, a prominent subfield of machine learning, is an innovative technology that emulates the operational mechanisms of the human brain in order to process data and generate meaningful information. Utilizing layered structures known as artificial neural networks, deep learning systems can self-learn and distil insights from expansive and complex datasets (Šećkanović et al., 2020). These layers of neural networks mimic the neural circuitry of the human brain and are responsible for transforming input data into an output decision or prediction, a process that necessitates progressive abstraction and pattern recognition (Kagiyama, Shrestha, Farjo, & Sengupta, 2019). Depth in deep learning reflects the number of layers through which the input data are successfully transformed, enabling the system to recognize and learn highly intricate patterns and associations across the dataset.

Deep Learning vs Traditional Machine Learning

Deep learning is often compared to traditional machine learning, given its shared roots in AI. However, key differences exist between the two technologies. Traditional machine learning algorithms, although powerful, often plateau in their performance with the addition of more data. In contrast, deep learning models thrive on big data, continually improving the accuracy and reliability as the volume of data increases. This unique attribute makes deep learning particularly effective for tasks that involve large volumes of data, such as image recognition, speech recognition, and natural language processing (Seetharam, Shrestha, & Sengupta, 2019).

Moreover, while traditional machine learning models require manual feature extraction, a process that can introduce human error and bias, deep learning models autonomously learn to extract relevant features from data, ensuring a more objective and comprehensive analysis (Krittanawong, Zhang, Wang, Aydar, & Kitai, 2017).

Advantages of Deep Learning in Medical Applications

Deep learning has found prolific applications within the medical field owing to its exceptional performance in critical tasks such as medical image analysis, electronic health record (EHR) data analysis, and prediction of disease progression. Leveraging its ability to extract complex features from high-dimensional data, deep learning models can provide a nuanced and precise analysis, thereby enhancing the accuracy and reliability of medical predictions and diagnoses (Dorado-Díaz, Sampedro-Gómez, Vicente-Palacios, & Sánchez, 2019).

Within the cardiology domain, the applications of deep learning are manifold. It has been successfully deployed to detect arrhythmias from electrocardiograms (ECGs), predict cardiovascular disease risk from imaging data, and forecast future cardiovascular events based on EHR data. These use cases demonstrate the potential of deep learning in a new era in cardiac care, enhancing predictive accuracy, improving patient management, and expediting the discovery of novel therapeutic strategies.

3. Technological Advances in Cardiac Diagnostics

Echocardiogram (ECO) Analysis and Interpretation through AI

Echocardiography (ECO) is a central element in the assessment of cardiac structure and function. In the contemporary healthcare landscape, AI's integration of AI into ECO analysis and interpretation has significantly revolutionized cardiac assessments by enhancing their accuracy, expediting processing speeds, and elevating the overall efficiency of the diagnostic process (Koulaouzidis et al., 2022).

Deep learning algorithms have been established as potent tools for automating the measurement and quantification processes associated with cardiac structures. These automated systems streamline clinical workflows and enhance the precision of cardiac abnormality detection, subsequently leading to more accurate predictions of clinical outcomes (Zhang et al., 2020). For instance, AI-based algorithms have shown remarkable precision in quantifying left ventricular ejection fraction, a pivotal parameter in assessing heart function. Such advancements facilitate early detection and prompt intervention of cardiac diseases, significantly improving patient prognosis and treatment outcomes (Manlhiot, van den Eynde, Kutty, & Ross, 2022).

Enhancement of Electrocardiogram (ECG) Readings using Deep Learning

Deep learning technology has brought considerable advancements to electrocardiogram (ECG) analysis, specifically in enhancing the detection and prediction of arrhythmias and various cardiovascular conditions. Deep learning algorithms can meticulously analyze minute details in ECG waveforms, which are often overlooked by human observers, to detect intricate patterns indicative of various cardiac pathologies (Itchhaporia, 2022).

Moreover, AI technology significantly augments traditional ECG readings by identifying subtle waveform changes that predict future cardiac events (Attia et al., 2019). This predictive ability provides a window for early intervention and strategic patient management, ultimately leading to improved patient outcomes.

Coronary Angiography: AI Integration for Superior Imaging

Coronary angiography, a crucial diagnostic tool for diagnosing and managing coronary artery disease, has also benefitted from AI integration. With AI, coronary angiography has enhanced image acquisition, reconstruction, and interpretation processes, leading to safer and more precise diagnoses (Howard et al., 2019).

Deep learning models can optimize contrast use and radiation dose, thereby reducing patient exposure to harmful radiation and contrast-induced nephropathy. Additionally, these models can reduce artifacts and improve the identification and characterization of coronary lesions, thereby enhancing the diagnostic accuracy (Tatsugami et al., 2019; Du et al., 2021). AI systems offer automated assessments of stenosis severity and plaque characteristics. Such data are valuable in formulating treatment plans and predicting future cardiac events, providing a comprehensive approach for managing cardiovascular diseases.

Table 1. Advancements in Cardiac Diagnostics Through AI Integration

Cardiac Diagnostics	Advantages with AI
Echocardiography (ECO)	Automated measurement and quantification of cardiac structures; Enhanced detection of cardiac abnormalities; Improved prediction of clinical outcomes
Electrocardiogram (ECG)	Enhanced detection of arrhythmias and various cardiovascular conditions; Improved prediction of future cardiac events
Coronary Angiography	Optimized contrast use and radiation dose; Reduced artefacts; Enhanced identification and characterization of coronary lesions; Automated assessment of stenosis severity and plaque characteristics

4. Harnessing Deep Learning in the Management of Chronic Cardiac Patients

Deep Learning in Remote Patient Monitoring

The consistent and precise monitoring of patients with chronic cardiac conditions is critical for preempting sudden cardiovascular events and effectively managing the disease trajectory. By incorporating artificial intelligence (AI) and deep learning into remote patient monitoring technologies, substantial potential to revolutionize patient management has been demonstrated. These advancements facilitate the improved assessment of pivotal parameters, such as vital signs, physical activities, and lifestyle habits correlated with cardiovascular health (Infante et al., 2021).

Deep-learning algorithms are used to process and interpret multiple streams of data, including those sourced from wearable devices and smartphone applications. By utilizing these algorithms, healthcare providers can potentially recognize the early signs of acute cardiac events or decompensation, facilitating swift interventions (Lopez-Jimenez et al., 2020). As such, deep learning is at the forefront of fostering dynamic, data-driven, and patient-specific healthcare delivery.

Deep Learning in Predictive Models for Clinical Decision-Making

Deep learning has shown remarkable proficiency in creating predictive models, aiding clinical decision making in the management of patients with chronic cardiac disease. These models excel at processing vast amounts of multidimensional, intricate patient data to predict various outcomes, including disease progression, probability of hospital readmission, and mortality rates (Seetharam, Shrestha, & Sengupta, 2019).

By equipping clinicians with tools to predict future clinical events, these models enhance decision-making processes, optimize treatment plans, and improve patient outcomes. Therefore, the integration of deep learning in clinical decision making represents a significant step towards the future of personalized medicine.

AI-Powered Personalized Care Plans

The integration of AI and deep learning has revolutionized the approach to creating personalized care plans for patients with chronic cardiac conditions. AI algorithms process extensive patient data including genetic determinants, lifestyle aspects, and concurrent medical conditions. By understanding individual risk factors and predicting personalized responses to various treatment strategies, these algorithms allow the creation of tailored care plans (Krittanawong et al., 2017).

Personalized care plans enhance the effectiveness of treatment strategies, mitigate side effects, and improve patients' quality of life. By individualizing healthcare delivery, these AI-powered plans provide a significant advantage in chronic cardiac patient management, propelling patient-centered care in the future.

Table2. Deep Learning Enhancements in Chronic Cardiac Patient Management

Chronic Cardiac Patient Management	**Advancements with Deep Learning**
Remote Patient Monitoring	Enhanced assessment of vital parameters; Early detection of acute cardiac events or decompensation; Facilitated prompt interventions
Predictive Models for Clinical Decision-Making	Improved forecasting of clinical outcomes; Optimized treatment plans; Elevated patient outcomes
Personalized Care Plans	Tailored treatment strategies; Mitigated side effects; Enhanced quality of life

5. Predicting and Diagnosing Cardiovascular Diseases: The Deep Learning Approach

Prognostic Models for Heart Failure

Advancements in deep learning methodologies have catalyzed the development of highly sophisticated prognostic models for heart failure (HF). These models were designed to assimilate a wide array of data points, including genetic variables, lifestyle behaviors, imaging studies, and laboratory findings, thereby capturing the multifactorial nature of HF (Chen et al., 2022). By offering comprehensive insights into disease progression, patient prognosis, and therapeutic response, these algorithms can guide the stratification of patients according to their risk and personalize their treatment strategies. This nuanced approach to HF management can optimize clinical outcomes and enhance the efficiency of healthcare resources (Rajkomar et al., 2018).

Prediction of Coronary Heart Disease

Deep learning has shown profound utility in accurately predicting the onset of coronary heart disease (CHD), an area in which early detection can significantly improve patient outcomes. Through comprehensive analyses of individual health records, genetic predispositions, and environmental influences, deep learning models can discern intricate patterns that may elude conventional analytics (Al'aref et al., 2019). Such predictive capabilities can aid in the early detection of CHD, facilitating timely therapeutic interventions, and reducing the risk of long-term complications, including myocardial infarction and stroke (Motwani et al., 2017).

Risk Stratification for Arrhythmias

In the arena of arrhythmias, deep learning has demonstrated the potential for developing robust risk stratification models. By dissecting complex ECG data, these models can predict the likelihood of patients developing a range of arrhythmias from atrial fibrillation to life-

threatening ventricular tachycardia (Hannun et al., 2019). This technological application has the potential to transform the clinical management of arrhythmias by guiding preventive strategies, personalizing therapeutic approaches, and enabling more focused monitoring of high-risk individuals, thereby mitigating the morbidity and mortality associated with these conditions (Raghunath et al. 2020).

AI and Cardiomyopathy

The diagnostic and management spectrum of AI extends significantly to cardiomyopathies. Deep learning algorithms capable of processing large volumes of diverse data sources, including echocardiography and cardiac magnetic resonance imaging, can detect early signs of cardiomyopathy and predict its clinical course (Narula et al., 2020). Through AI, clinicians can gain a profound understanding of the heterogeneous nature of cardiomyopathies, allowing them to devise more effective and individualized treatment plans to improve patient outcomes and quality of life (Alsharqi et al., 2018).

6. The Transformative Influence of AI in Interventional Cardiology

Robotic-assisted Cardiac Surgery

The rise in artificial intelligence has had a profound impact on the evolution of cardiac surgery, particularly in the realm of robot-assisted procedures. AI-infused robotic systems provide surgeons with unprecedented precision and control, thereby mitigating surgical risks and improving patient outcomes (Romiti et al., 2020; Manlhiot et al., 2022). Furthermore, AI algorithms are increasingly being leveraged for preoperative planning and are capable of digesting patient-specific data to predict potential complications and strategizing the optimal surgical approach. Such predictive capabilities enhance patient safety, potentially expedite recovery times, and increase the overall success rates of cardiac surgeries.

Deep Learning in Optimizing Percutaneous Coronary Intervention

Percutaneous coronary intervention (PCI), a nonsurgical procedure used to treat coronary artery stenosis, has substantially benefited from the integration of deep learning (Du et al., 2021; Howard et al., 2019). AI algorithms have shown remarkable competence in analyzing angiographic data to elucidate detailed information about lesion characteristics and guide optimal stent placement. Furthermore, deep learning models are adept at predicting the likelihood of post-PCI complications including restenosis, which significantly aids in risk stratification and post-procedure patient management. Therefore, the convergence of deep learning and PCI can lead to more personalized treatment, thereby enhancing patient outcomes and overall procedural efficacy.

AI in Vascular Health Risk Stratification and Management

The deployment of AI in vascular health risk management shows remarkable promise, particularly for predicting cardiovascular events, refining treatment strategies, and monitoring disease progression (Haq et al., 2022). Machine learning models, equipped to process an array of complex and high-dimensional patient data, encompassing genetic markers, clinical variables, and imaging data, can accurately identify high-risk individuals. Moreover, these models can predict the likely course of vascular diseases, significantly aiding in treatment planning and proactive disease management. AI can also help monitor patient adherence to prescribed treatments, analyze the effectiveness of various treatment strategies, and predict potential adverse effects. These applications contribute to a comprehensive and personalized

approach to vascular health management, potentially improving patient outcomes and healthcare efficiency.

7. Radiogenomics: Pioneering the Route to Precision Medicine in Cardiology

Augmentation of Cardiac Computed Tomography Angiography (CCTA) through AI Integration

The fusion of artificial intelligence with cardiac computed tomography angiography (CCTA) has revolutionized diagnostic precision and accuracy in cardiology. In particular, deep learning models are used to analyze CCTA images to discern and quantify the extent of coronary artery disease, estimate stenosis severity, and predict the likelihood of imminent adverse cardiac events with remarkable accuracy (Infante et al., 2021). Furthermore, AI algorithms are capable of enhancing CCTA image quality, which reduces the need for repeated scans and consequently minimizes patient exposure to radiation (Tatsugami et al., 2019).

Machine Learning: Enhancing the Efficacy of Cardiac Magnetic Resonance (CMR) Imaging

Machine learning, particularly deep learning, has demonstrated significant potential for augmenting the utility of cardiac magnetic resonance (CMR) imaging. Automated algorithms can efficiently execute tasks such as segmentation and quantification of myocardial volumes as well as identify disease patterns. These capabilities not only enhance accuracy and speed but also alleviate the demanding workload of clinicians (Hahn et al., 2019; Hahn et al., 2022). Moreover, machine learning models can use CMR data to predict patient outcomes, which substantially assists in risk stratification and tailoring personalized treatment plans.

Radiogenomic Markers in Cardiology: Current Developments and Future Prospects

Radiogenomics, the intersection of radiological characteristics and genetic variations, offers a promising pathway for precision medicine in cardiology. AI models are increasingly being leveraged to correlate radiological features derived from cardiac imaging with genomic data to identify unique radiogenomic markers of cardiovascular diseases. These markers have the potential to predict disease risk, progression, and response to therapy at the individual level (Dorado-Díaz et al., 2019; Krittanawong et al., 2017). As research in this nascent field continues to evolve, the future may see widespread integration of radiogenomic markers into routine clinical practice, spearheading a new era of personalized medicine in cardiology.

8. Ethical and Legal Considerations

AI and Patient Confidentiality

As AI continues to revolutionize cardiology, patient confidentiality concerns have escalated. AI algorithms depend on large volumes of sensitive health data, increasing the risk of data breach and misuse. Therefore, the implementation of robust data security protocols and encryption methods is critical for maintaining data security (Koulaouzidis et al., 2020; Koulaouzidis et al., 2022). Anonymization or pseudonymization of patient data prior to analysis offers further protection. Moreover, patients should give informed consent for the use of their data in AI applications, and they should fully understand how their data are used, considering this as a pivotal ethical aspect (Manlhiot et al., 2022; Nakamura & Sasano, 2022).

Legal Implications of AI in Cardiology

The integration of AI into cardiology raises complex legal questions. For example, when an AI algorithm errors, leading to patient harm, who bears legal responsibility? The healthcare provider, AI system developers, or institution that approved its use? There is an urgent need for comprehensive legal frameworks to address these questions to ensure accountability and instill trust in AI applications in cardiology (Haq et al., 2020; Haq et al., 2022). Moreover, the development of global standards for the validation and approval of AI tools is necessary to ensure their safety and efficacy.

Decision-making and Responsibility

AI can assist clinicians in decision-making but cannot substitute human judgment. Clinicians bear the ultimate responsibility for patient care. They should make informed decisions based on AI-generated insights combined with their professional expertise, clinical guidelines, and patient preferences (Lopez-Jimenez et al., 2020; Mathur et al., 2020). It is also crucial to consider that AI systems can harbor biases inherent in their training data that can influence their predictions and recommendations. Thus, AI should support, rather than replace, the clinician's role in patient care (Siontis et al. 2021; Shu et al. 2021).

AI Transparency and Explainability

Transparency and explainability are two crucial ethical issues in AI. AI models often operate as "black boxes," producing results without a clear explanation of the process. This lack of transparency can hinder the clinicians' understanding and acceptance of AI-based decisions (Romiti et al. 2020). Thus, enhancing the explainability of AI models and how they arrive at their decisions is necessary to promote trust and understanding of these systems among clinicians and patients alike (Šećkanović et al., 2020).

Bias and Fairness in AI

There is also a concern that AI models can perpetuate and amplify the existing biases in healthcare. Biases can occur if AI models are trained on datasets that are not diverse or representative of the population to which they will be applied. This can lead to unfair treatment outcomes and potentially exacerbate health disparities (Attia et al. 2019; Itchhaporia et al). 2022). Therefore, ensuring the diversity and representativeness of training data is a key ethical consideration in AI-based cardiology.

9. Future Trajectories and Challenges in Cardiac AI

Deep Learning: Unfurling the New Age of Cardiac Research

As we venture further into the AI landscape within cardiology, the role of deep learning as a research focal point is anticipated to expand. It has the capacity to process and decipher large and intricate datasets, which can be employed to establish predictive models, enhance diagnostics, oversee disease progression, and fine-tune individualized treatment strategies (Šećkanović et al., 2020; Kagiyama et al., 2019). Present and future research are expected to traverse more specialized applications of deep learning, like the interpretation of echocardiograms, detection of rare cardiac disorders, and prediction of patient responses to novel treatments.

Hurdles in the Integration of AI into Cardiology

Notwithstanding the exhilarating potential of AI in cardiology, several significant obstacles persist. Issues regarding data privacy and security, legal considerations, and the

requirement for rigorous validation of AI applications prior to their clinical integration remain prominent challenges. Furthermore, integrating AI into the existing healthcare infrastructure poses its own complexities, necessitating considerable resources and training. The possible biases in AI algorithms and their "black-box" nature – the challenge in understanding the reasoning behind their conclusions – could potentially deter widespread adoption (Dorado-Díaz et al., 2019; Siontis et al., 2021).

AI-Powered Personalized Cardiology: The Next Chapter

The dawn of personalized medicine, driven by artificial intelligence (AI) and machine learning, can redefine cardiac care. AI's ability of AI to analyze extensive datasets can assist in predicting individual risk profiles, personalizing treatment plans, and monitoring patient responses in real time. AI can augment the comprehension and management of diverse cardiac diseases by facilitating the identification of genetic predispositions and categorizing patient subgroups based on various clinical, environmental, and genetic factors. Future research should emphasize the creation of precise and personalized AI tools and their integration into everyday clinical practice (Cheng et al., 2020; Haq et al., 2022).

Real-time Monitoring and AI: The Future Pulse of Cardiology

The introduction of wearable technology and remote monitoring devices has transformed cardiac care by facilitating continuous real-time data collection. AI's role of AI in this transition is pivotal, as it assists in the analysis of large-scale, high-frequency data to detect early disease markers, monitor disease evolution, and evaluate treatment responses. This may culminate in prompt intervention, improved patient outcomes, and reduced healthcare expenditure. Future research should aim to develop and validate AI algorithms dedicated to real-time data analysis and their amalgamation with wearable and remote monitoring systems (Steinhubl et al., 2020; Steinhubl et al., 2021).

Bridging Health Disparities: A Potential Role for AI in Cardiology

AI bears the potential to address disparities in healthcare. Through population-wide data analysis, AI can help discern patterns of inequalities in cardiac care and outcomes, reveal underlying social determinants, and inform targeted interventions. However, the effectiveness of AI in this context depends heavily on the quality and representativeness of the data. Efforts should be channeled towards the inclusion of diverse and underrepresented groups in AI research, ensuring that the advantages of AI-driven interventions are equally dispersed (Itchhaporia et al., 2022; Lum et al., 2022).

10. Conclusion

Recapitulation and Final Remarks

Artificial intelligence, particularly deep learning, has emerged as a transformative force in the field of cardiology. Its applications span various aspects of cardiac care, encompassing disease prediction, diagnosis, interventional procedures, and personalized treatment plans. The integration of AI with cardiology has also paved the way for radiogenomics, thereby offering new avenues for precision medicine. However, it is essential to address the ethical and legal considerations associated with AI adoption and the challenges that accompany its implementation (Bhadri et al., 2017; Bhadri et al., 2022).

Future Perspectives

Looking ahead, deep learning is poised to become an indispensable component of cardiac research and clinical practice. Ongoing advancements in AI technology are likely to enhance the transparency, reliability, and user-friendliness of AI tools. Collaborations across disciplines, including clinicians, computer scientists, ethicists, and policymakers, will play a vital role in tackling the challenges and fully harnessing the potential of AI in cardiology. The ultimate aim is to leverage AI to deliver safer, more efficient, and personalized cardiac care, leading to improved patient outcomes and a higher quality of life (Lopez-Jimenez et al., 2020; Nakamura & Sasano, 2022). By embracing the possibilities offered by AI, the field of cardiology can continue to evolve and embrace the advancements in the digital era, ultimately benefiting patients and healthcare providers alike.

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Current Approaches In Maxıllary Sınus Augmentatıon Technıques

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Introduction

The maxillary sinuses are the largest of the paranasal sinuses and are cavities containing approximately 12-15 ml of air in adults (Chanavaz, 1990). The sinus floor is close to the nasal cavity and its upper border forms the floor of the orbit, while its apex is a pyramidal structure towards the zygomatic process (Testori, 2011). The sinus floor extends from the region of the maxillary premolar-canine teeth to the tuber, usually the part closest to the tooth roots is in the region of the maxillary first molar teeth (Woo & Le, 2004). When implant treatment is planned in the maxillary posterior region, the location of the sinus floor should be considered due to the close relationship between the maxillary posterior field and the maxillary sinus. After tooth loss in the maxillary posterior region, the bone resorption process begins. At the beginning of resorption, the width of the alveolar bone first decreases. This resorption process then continues in all directions. This occurs more rapidly in the posterior maxilla than in other parts of the mouth (Pietrokovski, 1975).

Sinus augmentation was first described by Boyne and James (Boyne & James, 1980) and Tatum (Tatum Jr, 1986), and its various modifications have emerged since then. Sinus augmentation techniques in edentulous areas give successful results for implant rehabilitation with correct treatment planning (Tatum Jr, 1986). The Schneiderian membrane is the mucous membrane that surrounds all the walls of the maxillary sinus cavity (Wen & et al., 2015). It consists of pseudo-ciliated cylindrical epithelium and periosteum covered with highly vascularized connective tissue (Testori, 2011; Wen & et al., 2015). Stem cells are located in the periosteal layer and they have osteogenic potential (Kim & et al., 2009). Sinus membrane thickness is a factor affecting sinus perforation (Janner & et al., 2011; Shanbhag & et al., 2014). During surgical procedures, Schneiderian membrane perforation is more likely to occur in thin mucosa (<3 mm), while thicker mucosa is more resistant to instrumentation (Rapani, Rapani & Ricci, 2016; Wen & et al., 2015). Although there are different opinions about the normal thickness of the sinus membrane, the average membrane thickness is considered to be approximately 1 mm (Çakur, Sümbüllü & Durna, 2013; Rancitelli & et al., 2015). In general, the membrane is thicker in men than in women, and the thickness decreases from anterior to posterior in both sexes (Kalyvas & et al., 2018).

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Diagnosis in maxillary sinus augmentation

Bone height is a factor of primary importance when implant treatment is planned for the atrophic posterior maxilla. Insufficient height for standard size implants may result from sinus pneumatization or alveolar crest resorption (Chiapasco, Casentini & Zaniboni, 2009). Following tooth loss, resorption of the posterior maxilla usually progresses in all three dimensions. As the resorption progresses, especially vertical and horizontal bone losses are more pronounced. Sinus augmentation may be chosen as an adjunct procedure in mild to moderate resorption. However, it should be noted that sinus augmentation alone may not create ideal tissue contours. In severe resorption cases, as the extent of resorption increases, a complicated approach involving sinus lift operations with block bone grafts should be considered (Chiapasco, Casentini & Zaniboni, 2009). Therefore, when considering implant treatment in the atrophic posterior maxilla, not only the existing bone volume but also the three-dimensional relationship between the arches should be evaluated.

Classification of maxillary sinus augmentation techniques

In general, there are 4 main sinus lift techniques:

a. Lateral approach sinus lift technique

The lateral window technique is a widely used augmentation procedure that allows the placement of an appropriately sized implant in the posterior region of the maxilla, where bone quality is usually poor. In cases where the sinus floor anatomy is horizontal and the residual bone height is 6 mm or less, and the sinus floor anatomy is oblique, the lateral window technique is applied regardless of the residual bone height. The first step is to lift the full thickness flap in the maxilla. A high speed round bur/piezosurgery diamond rond bit can then be used to create a bone window. The Schneiderian membrane should be fully elevated to the desired height for bone graft materials (Boyne & James, 1980; Tarnow & et al., 2000). Based on the residual bone height and the length of the implant to be placed, it is decided whether the implant should be placed at the same time as the sinus lift procedure. Generally, in cases where the residual bone height is 5 mm or more, the single-stage lateral window technique is applied if the primary stability of the implant can be achieved, while the two-stage technique is selected when the residual bone height is less than 5 mm.

Traditional lateral window technique

Anesthesia

Local anesthetics with adrenaline are preferably used.

Incision (flap design)

The mucosal incision should consist of 1 horizontal incision and 2 relaxing vertical incisions. Vertical relaxing incisions are made in the mesial and distal extension of the horizontal incision. The mucoperiosteal flap is raised so that the bone is approximately 5 mm above the window. This flap design ensures safe handling of suture materials.

The design of the bone window

The borders of the bone window are determined according to the width of the area where the implant reconstruction is planned and the graft is planned. The shape of the bone window

can be rectangular, square or oval shaped. During osteotomy, an incision should be made so that the lower border of the window is 4 mm above the sinus floor. The main factor determining the upper limit of the incision is the position of the Alveolar Antral Artery. The upper border of the window is prepared to be below Alveolar Antral Artery.

Preparation of the bone window

High-speed rotary instruments are used when preparing the bone window. High speed saves time but is more technically accurate. 4, 6 or 8 diamond round burs are used under copious irrigation to outline the osteotomy (window).

The osteotomy is deepened with light sweeping movements until you can see the color of the underlying membrane. The bone incision is continued until the window is completely separated from the sinus membrane as a whole. The mobility of the window is checked with hand tools, and osteotomy is continued if there are points of connection. The bone window can be prepared in different shapes such as round, square, rectangular, or it can be completely milled during bone incision.

Bone window

1. Tatum advocates careful elevation of the bony window with the membrane to fracture it so that it lies over the graft materials and forms the roof of the sinus grafts (Tatum Jr, 1986).

2. *The wall off technique* involves the complete separation of the bone window from the surrounding wall with sinus elevators.

Elevation of the sinus membrane

The sinus membrane should be separated from the lateral borders of the sinus with hand tools/devices. The membrane in the apical part of the sinus cavity and in the mesial and distal directions is slowly separated from the bone surface. After the membrane is released, it is elevated backwards and upwards in the sinus cavity. The most important point during elevation is that the elevators should always be in contact with the bony walls of the sinus cavity. Elevation should continue until the sinus membrane reaches the inner wall of the sinus cavity. It should be ensured that the membrane is lifted high enough to place an implant of the appropriate length.

Bone graft materials and barrier membrane

Autogenous grafts, allografts, xenografts and alloplastic graft materials can be used in maxillary sinus augmentation. The most preferred alloplastic materials are beta-tricalcium-phosphate and platelet-rich plasma (PRP) and platelet-rich fibrin (PRF). Medium-sized particle sizes and non-sharp edges, hydraulic properties, and easy application are the features sought in the graft material to be selected in sinus augmentation procedures. In order for the graft particles to be carried as a whole, they must be moistened with saline or PRP/PRF obtained from the patient's own blood. During the operation, autogenous bone grafts can be collected with bone scrapers. Collected autogenous grafts can be mixed with xenogenic or allogeneic materials to increase the osteogenic potential of graft materials.

There are studies showing that the use of a barrier membrane to close the lateral window can increase the implant success rate (Tawil & Mawla, 2001; Wallace & Froum, 2003). To close the window, a suitable barrier membrane is selected for the case. The membrane is prepared in such a way that it completely closes the entrance window and remains on the healthy bone tissue. The smooth surface of the membrane is positioned in such a way that the rough surface is adjacent to the mucosa and its surface is moistened. While horizontal matrix sutures are usually sufficient for the fixation of the membrane, in cases where immobilization cannot be achieved, the membrane should be fixed at four points with fixation pins. While placing the graft, care should be taken not to narrow the maxillary sinus ostium (Hunter IV & et al., 2009).

Primary closure of the flap

The suture techniques used during flap closure help passively approach the edges of the flaps and keep the flap closed in the early stages of healing. During suturing, additional damage to tissues should be avoided. In cases where vertical/horizontal augmentation is not performed, the suture is started from the flap corners. In cases where vertical/horizontal augmentation is performed with the lifting process, the flap should be released with incisions made from the deepest part of the flap to the periosteum and closed without tension. The flap should be tension-free and primarily closed to prevent microbial contamination of the graft. It is recommended to remove the sutures approximately 10-14 days after the procedure.

Post-op radiographic control

Panoramic x-ray is recommended to view the augmented area after the operation. The graft around the elevation area in the sinus cavity should be observed in a clear and well-defined manner. If there is thought to be a problem with the elevation, it can be checked with cone beam computed tomography. In doubtful cases, the patient should be followed up clinically and radiographically at regular intervals.

Piezo assisted sinus lift method

Sinus lift technique performed with a piezosurgery device is superior to rotary instruments in terms of preventing Schneiderian membrane perforation. While corticotomy and elevation are performed with special tips of the piezosurgical device, other procedures are just like in traditional methods.

Lateral approach sinus kit (LAS-KIT®) method

The LAS-KIT® method is a drill system developed by Ostemm® company to provide sinus elevation without creating membrane perforation on the lateral wall of the sinus. The set consists of a set of burs, called dome and core, used to prepare the lateral window. The dome bur completely lifts the lateral wall of the sinus to reach the membrane. Thanks to its groove design, the dome bur does not damage the soft tissue while abrading the bone tissue and minimizes direct contact with the membrane. Core bur with a round-shaped cutting edge protects the bone wall and allows access to the membrane only from the edge of the membrane. The stopper system of 6 different lengths, designed to prevent excessive corticotomy and soft tissue damage, provides more precise control over the bur. Large dome and core burs are used to widen the bony window. With the combination of three macro blades and several micro blades, LAS-KIT® burs offer various usage options depending on the oral anatomy and surgical plans, thanks to their flexible design. After the bone incisions, the process is continued with

sinus membrane elevators and augmentation is performed (https://www.osstemuk.com/surgery-kits/las-kit-implantology-sinus-lifting/).

Sinus lateral approach kit (SLA-KIT®) method

The SLA-KIT® method consists of a drill system developed by NeoBiotech® and a set containing membrane elevators to provide sinus elevation without membrane perforation on the lateral wall of the sinus. The process begins by preparing a guide point on the lateral wall of the sinus with a marking bur and elevates the bone tissue without creating membrane perforation, as in the LAS-KIT® system (https://www.neobiotech.hu/index.php/sla-kit-sinus-lateral-approach/).

b. Transcrestal approach

The advantage of the transcrestal technique is its reduced invasiveness and, consequently, its significantly lower morbidity than the lateral window technique. However, with this technique, bone height can only be increased by 2-4 mm and therefore requires more available bone volume than the lateral window technique (Jensen & Terheyden, 2009). In other words, the transcrestal sinus lift technique is not suitable for severely atrophic cases and should only be used when primary implant stability can be achieved. The anatomy of the sinus floor should also be included in the pre-surgical evaluation to decide on the technique. In cases where the horizontal and residual bone height of the sinus floor anatomy is less than 6 mm, the sinus lift technique with crestal approach can be applied. Implants can be placed at the same time as the sinus lift procedure.

Summer's technique (osteotome technique)

The crestal approach uses instruments called osteotomes to prepare the implant socket, creating a controlled "green tree fracture" at the sinus floor and enabling new vertical bone formation. This method, in which an osteotome of varying diameters is used to elevate the residual bone, was named the osteotome technique by Summer (Summers, 1994). Osteotomes are conical in shape and are indicated for surgical techniques where the residual bone height is 5-6 mm.

Application of the technique

Soft tissue incision is made, preferably after anesthesia is provided with adrenaline local anesthetics with adrenaline. The mucosal incision consists of 1 horizontal (crestal) incision and the full thickness flap is raised.

The bone incision in all sinus lift methods with crestal approach is no different from the implant socket prepared for implant placement. The distinguishing point here is the depth and width of the socket. First of all, marking is made on the alveolar crest with guide burs. Then, the socket is deepened with a twist drill until 1-2 mm is left to the sinus floor. The socket is enlarged with a thick twist bur while remaining at the same socket depth. This width provided by the bur should be thicker than the diameter of the thinnest osteotome in the osteotome set. From this stage, concave (D1-D2 bone) or convex (D3-D4 bone) osteotomes are selected according to the bone density and the process continues. A fracture fragment the size of the osteotome tip is created at the base of the sinus by applying vertical force to the osteotomes with hammers in the superior direction. During hammering, it should be observed that the osteotome is moving in the socket and the depth should be checked with the lines on the

osteotome. In D1-D2 bones, while the feeling of hard ending with osteotomes is continued during the impact, this feeling disappears at some point and the hammer moves freely in the socket for a few mm. At this time, a change in the deep sound of the socket is noticed, which is an indication that a fracture has occurred in the bone at the base of the socket. While hammering in D3-D4 bones, a soft ending is always felt, the bone sound never changes. After the desired elevation is achieved, the implant socket is enlarged according to the planned implant diameter with osteotomes or implant burs, depending on the bone density. If implant burs are to be used, care should be taken to deepen 1-2 mm to the sinus floor. Since the integrity of the sinus floor is not impaired after the technique, grafting is generally not needed.

Crestal approach sinus kit (CAS-KIT®) technique

CAS-KIT® has been specially designed by Ostemm® to easily and safely lift the maxillary sinus membrane with a crestal approach. The CAS-KIT® set consists of CAS burs with stopper system for performing osteotomy, hydraulic lifter for membrane elevation, depth gauge and instruments designed for graft adaptation. The tip of the CAS-KIT® burs is designed to collect the cortical bone from the sinus floor and provide Schneiderian membrane elevation.

After preoperative clinical and radiological evaluations, the full thickness flap is raised with a crestal incision. Socket deepening is provided until 1 mm is left to the sinus floor. By increasing the stopper size, the bone at the base of the sinus is milled with a drill. Cortical bone collected at the tip of the bur provides elevation of the Schneiderian membrane. With CAS-KIT® burs, 1-2 mm elevation can be achieved by preserving the integrity of the sinus membrane. The main membrane elevation is made with the hydraulic lifter and the full adaptation of the lifter into the socket. The hydraulic lifter is used with saline solution. Usually 0.2-0.3 cc of saline solution is injected slowly to elevate the membrane by 3 mm. After checking whether there is membrane perforation after sufficient elevation, the procedure is completed by placing the implant. In cases where graft use is considered, autogenous grafts without antigenic properties should be preferred against the possibility of perforation. The CAS-KIT® technique is not recommended where the sinus floor (including the septum) has complex morphology (https://www.osstemuk.com/wp-content/uploads/2019/12/Osstem-CAS-KIT-Brochure.pdf).

Sinus crestal approach (SCA-KIT®) technique

The SCA-KIT® system is a closed sinus lift technique developed by NeoBiotech. The system has a special bur design called S-Reamer. Just like the CAS-KIT® system, S-Reamer burs work with a similar system that allows bone aggregation at the tip, thanks to its special thread structure. The system consists of SCA-KIT burs (S-Reamer) with stopper and 4 burs, a twist burs, bone condenser, depth gauge, graft carrier and bone expander. The S-Reamer always leaves a thin layer of bone between the drill and the membrane during drilling, so it never comes into direct contact with the sinus membrane. This reduces the possibility of perforation and ensures safe use (https://global-uploads.webflow.com/62faf8ad9cb0ad5f875ac350/62faf8ad9cb0ad7c005aca5b_Leaflet_SCA%20Kit.pdf).

Osseodensification technique

The osseodensification technique is a system introduced by the Versah® firm founded by Dr. Huwais. The purpose of this system is to create a new instrument and procedure for preserving healthy bone during osteotomy rather than removing existing bone to provide space when performing osteotomy with conventional burs. The procedure is performed using instruments invented by Dr. Huwais, which he calls the Densah bur kit. In contrast to bone removal, with Densah burs the bone is reversed at 800-1500 Rpm and combined with irrigation

hydrodynamically densifies bone through autografting or osseodensification. As a result, a condensed osteomy site is created. This is very important for primary stabilization and early loading of placed implants.

After preoperative clinical and radiological evaluations, a crestal soft tissue incision is made, and the buccal and palatal flaps are relieved. Socket deepening is performed until 1 mm is left to the sinus floor. At this time, the traditional milling method is used, then the narrowest Densah bur is used. With the reverse rotation of the Densah burs, resistance is felt in the socket, so the burs should be guided inside the socket with back and forth movements. The bur size can be increased until the desired depth is achieved, but a maximum of 3 mm sinus elevation can be achieved with Densah burs. After the elevation, the implant is placed and the operation is completed (Huwais & Meyer, 2017).

Sinu-Lift® kit

Consisting of a disposable set, this kit consists of a hand-rotating Sinu-Drill bur with self-tapping, 3 mm and 4.2 mm curettes, a handpiece for graft placement, and a 3.2 mm diameter bur system for osteotomy.

After the buccal and palatal flaps are raised, the socket is deepened with a 2 mm diameter drill until 1 mm is left to the sinus floor. Then, the osteotomy diameter is expanded with a 3.2 mm drill. It is rotated by entering through the osteotomy line with the Sinu-Drill bur. When Sinu-Drill contacts the sinus membrane, the green ring on the bur starts to turn empty. After this stage, membrane elevation is achieved with yellow and blue curettes, respectively. The graft is sent through the socket and positioned under the sinus membrane, and the procedure is completed by placing the implant (Parthasaradhi & et al., 2015).

SinCrest® technique

SinCrest® burs, developed by META®, provide a guiding drilling area in the alveolar bone as close as possible to the maxillary sinus membrane. The SinCrest® manual osteotome is designed to provide controlled fracture of the base of the bone through a 0.5 mm stepwise advance. The probe incorporated into the SinCrest osteotome allows elevation of the maxillary sinus without causing perforation of the sinus membrane. The SinCrest® technique can be used in the presence of residual bone ranging from 5-11 mm (Borgonovo & et al., 2016).

Antral membrane balloon elevation (AMBE)

The technique is based on the principle of elevating the sinus membrane by inflating a tiny balloon or filling it with saline. After access to the sinus membrane is achieved, the membrane is elevated towards the medial wall. The advantages of this technique are limited incision, small window incision, removal of the sinus membrane with minimal trauma, and low perforation and complication rates (Soltan & Smiler, 2005).

Cosci technique

This technique is a modified version of the crestal approach technique. Different sizes of burs are used in the technique. Thanks to the tip design of the burs, the sinus floor is removed without breaking, and the perforation of the sinus membrane is prevented. According to Cosci and Luccioli, the Cosci technique requires approximately 10 minutes less time than the Summers technique (Cosci & Luccioli, 2000).

Internal sinus manipulation

The technique is an alternative crestal sinus augmentation method developed to facilitate sinus floor augmentation while reducing treatment morbidity. The technique can be performed with or without a full thickness flap lift. Osteotomy is performed with a surgical pilot drill and twist drill until 1-2 mm is left to the sinus floor. The bone at the base of the sinus is fractured by osteotomes. With internal lift elevators, the sinus membrane is elevated without losing bone support. With a blunt-ended depth gauge, membrane integrity is checked and the extent of elevation measured. The bone at the base of the sinus is broken with osteotomes used in the closed sinus lift technique. Specially designed membrane elevators, one with a disc shape and the other with an angled neck, are used in osteotomy. With these elevators, the sinus membrane is moved in the lateral and superior directions. Sinus membrane elevation is achieved by using disc-shaped and angled neck internal sinus lift elevators. Then the graft is placed and the desired position of the membrane superiorly is achieved (Yamada & Park, 2007).

Trephine core technique

An osteotomy is performed with a trephine bur with back and forth movements until 1-2 mm is left to the sinus floor. The outer bone cortex is gently removed to avoid perforation of the membrane; This is important because the membrane can then be repositioned on the graft or crushed to be used as graft material. The exposed membrane is then elevated from the sinus floor using osteotomes. The mucoperiosteal flap is repositioned and closed primarily (Raja, 2009).

The technique has advantages such as reduced time required for osteotomy and precise osteotomy, as well as negative aspects such as limited approach due to the angulation of the trephine burs.

c. Palatal sinus lift (WOLPE)

In the region of the premolars, a full-thickness flap is raised with a palatal crestal and oblique incision to reach the palatal wall of the maxillary sinus. Since no distal incision is made, blood flow from the greater palatine artery is provided uninterruptedly. Bone window osteotomy is performed using a piezosurgical device for palatal sinus lift. Following bone window osteotomy, the sinus membrane is elevated with sinus lift elevators.

Advantages of the technique; the absence of postoperative swelling, being a fast applicable procedure with low complications, low scar tissue formation during the recovery period, positioning of the graft more palatal, not requiring the use of membranes for graft stabilization, and using prosthesis immediately in the postoperative period since there are no muscular structures in the operation area (Vacher, Pavy & Ascherman, 1997). In addition, in this technique, thanks to the mesial position of the incision, the flap is also fed by the branches of the greater palatine artery (Piehslinger & et al., 1991).

Disadvantages of the technique; difficulty in seeing the surgical field, limited sinus lift, difficulties in flap lifting due to the structure of the palatal mucosa.

d. Computed tomography (CT) assisted approach

It is a radiographic sinus lift technique introduced in an article published by Matern JF et al. in 2014 (Matern & et al., 2016). In order to apply this technique, the residual alveolar bone height should be at most 5 mm. The process is managed using computed tomography.

The technique consists of 4 main steps.

Approach: The upper lip is retracted and a flapless 14.5 Gauge OstyCut needle is manually inserted mesial to the canine tooth parallel to the sinus floor. The progression of the bone needle towards the anterior alveolar maxillary trabeculation is followed under CT support.

Osteotomy: A trocar is placed 8 mm anterior to the maxillary sinus. To prevent any perforation, the needle is advanced until approximately 3 mm of trabecular bone contact is achieved. With the blunt end of the needle, a bone window is prepared close to the sinus membrane.

Lift: Sinus lifting procedure is performed with diluted contrast ionized liquid. On tomography, sinus membrane elevation is observed as a dome. To achieve gradual membrane elevation, this procedure is repeated 3-4 times.

Filling: After elevation, the sinus cavity is filled with diluted collagen sponge material. The absence of a dome shape or maxillary mucosal elevation suggests perforation.

Conclusion

Maxillary sinus augmentation for implant reconstruction of the posterior maxilla is a predictable surgical procedure that requires fulfillment of a number of criteria for optimal results. Planned preoperative clinical and with cone beam computed tomography assessment, including appropriate patient selection, is critical to the success of this surgery. Factors to be evaluated include the presence of ostiomeatal complex and healthy paranasal sinuses. Good surgical technique is important, including complication management. Implant failure, especially after several years, is often due to deficiencies in treatment planning or poor oral hygiene. Although complications and infections are not common in sinus augmentation surgery, they should be appropriately addressed by the treating physician. Well-treated complications will provide a highly predictable and successful long-term outcome.

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Digestive System Anatomy in Rats

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Introduction

The nutrients and energy necessary for the survival of the living thing, growth, and repair of worn-out cells and tissues are obtained as a result of the digestion of the foods that are taken. Ingested foods progress by undergoing changes in the digestive tract with mechanical, enzymatic, chemical, and bacterial effects. The secretions of the pancreas, liver, stomach, and small intestines are also very important as secretion factors in the change of nutrients in the digestive system. In order for nutrients to be used by cells and organs, they must be split to the extent that they can be mixed with blood and lymph as a result of mechanical and chemical digestion. The main aim of the digestive system organs is to break down the nutrients taken into building blocks and make them absorbable from the intestines.

The best absorption of digested nutrients from the intestines depends on the size of the inner surface of the intestine. The larger the lining of the intestine, the better the absorption. Absorption is increased by glove-like mucous membranes called villi, which line the inner surface of the intestine.

We can briefly summarize the functions of the digestive system organs in rats as follows;

The first part of the digestive system is the lips (labia). The lips are responsible for capturing food and conveying it to the oral cavity. The tongue (lingua) is in charge of mixing food. The saliva secreted by the salivary glands helps to create lubrication in the mouth and to moisten and soften the food taken. The esophagus is a tubular organ that allows food to pass through the pharynx and reach the stomach (ventriculus). The food coming from the esophagus is stored in the stomach and subjected to chemical digestion with digestive enzymes produced by softening. The intestines (intestinum) is the part of the digestive tract that starts from the stomach and ends at the anus.

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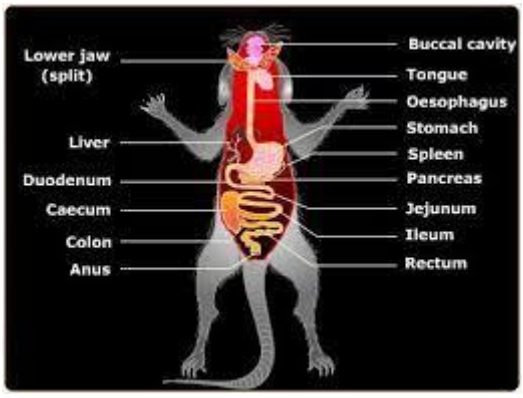

Figure 1. Diagram of digestive system organs in rats (Anonymous 1)

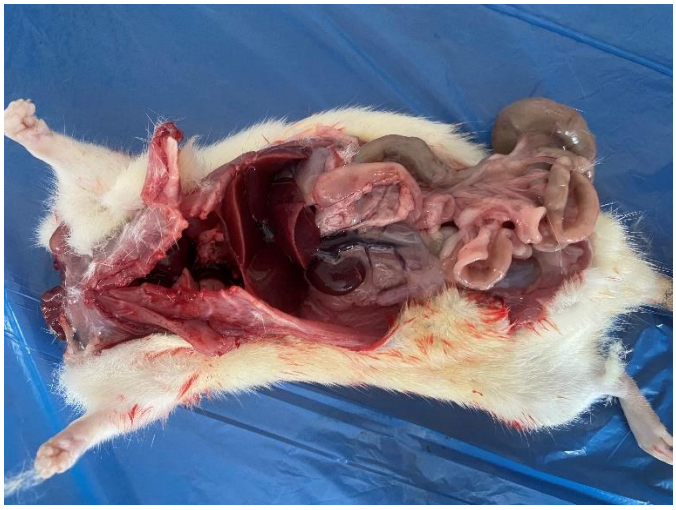

Figure 2. Ventral view of digestive system organs in rats

Oral cavity (Cavum oris)

The oral cavity of rats is divided by the labium superior having a funnel-shaped canal extending from the incisive teeth to the incisiv papillae and folding into the oral cavity. Communication between these two parts is provided by the muscle called musculus transversa palatini (Kutuzov and Sichher 1952).

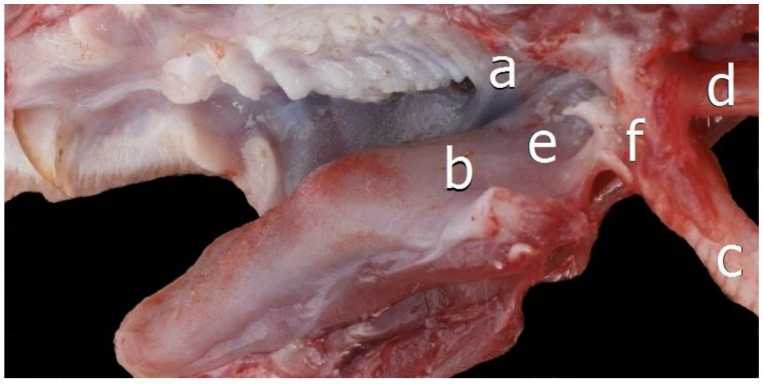

Figure 3: *Oral cavity in rats (a: soft palate (palatum molle), b: tungue root (radix linguae), c: trachea, d: esophagus, e: aditus pharyngis, f: larynx) (Anonymous 2)*

Lips (Labia oris)

Rats have pointed muzzles and truncated superior labium (Anonymous 2).

Cheek (Bucca)

There is no clear boundary between the buccal vestibul and the pharynx. Therefore, these two structures together are considered as the buccopharyngeal cavity (Anonymous 3).

Teeth (Dentes)

The dental formula and features of the teeth are the same as in other myomorph rodents. However, at rest, the mandibular incisors are located just behind the maxillary incisors. Coronas of mandibular incisors are about three times longer (Gültiken 2010). Cubs are born without teeth. In particular, incisive teeth do not have roots and continue to grow throughout their lives. Therefore, it must be gnawed and rasped so that it does not grow too long. There are 16 teeth in total. There is a gap called diastema between the cutting and chewing teeth (Anonymous 2). The elongation of the teeth is shaped in proportion to their wear, that is, the tooth lengths are constant. When the tooth is broken or malocclusion is formed, the rate of tooth elongation increases 2-3 times (Gültiken 2010).

Palate (Palatum)

In rats, the palatum has an indistinct raphe palati along the median line and its entire length. This division divides the palatum durum into four different parts. The oral atrium root consists of the antemolar region anterior to the molars, the intermolar space extending posterior to the molars and last molars, and the postrugal space between the palatum molle and the palatum state (Kutuzov and Sicher 1952).

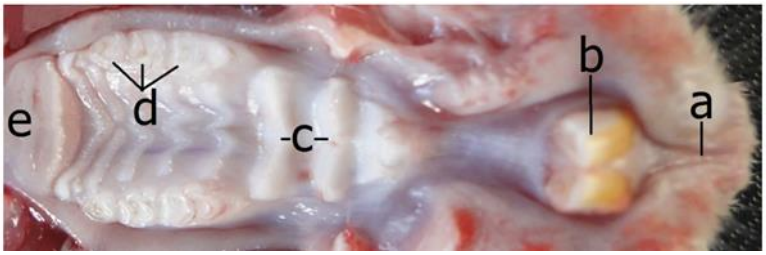

Figure 4: Palatum in rats (a: philtrum, b: incisive teeth, c: rugae palati, d: molars, e: soft palate (palatum molle) (Anonymous 2)

Floor of the oral cavity

The mandible is strongly fused with a fibrous symphysis and the connective tissue between the two mandibles forms the floor of the oral cavity (Anonymous 2).

Tonsils (Tonsilla)

Rats do not have tonsils. But NALT is found. (Casteleyn et al. 2011).

Tongue (Lingua)

In rats, the tongue is approximately 30 mm long and 8 mm wide from the anterior tip to the epiglottis. On its dorsal surface, a ridge rich in taste and mechanical papillary called torus linguae is observed (Gültiken 2010). Dorsum linguae is covered with papilla filiformis. Radix lingua has a single papilla vallata (Anonymous 2).

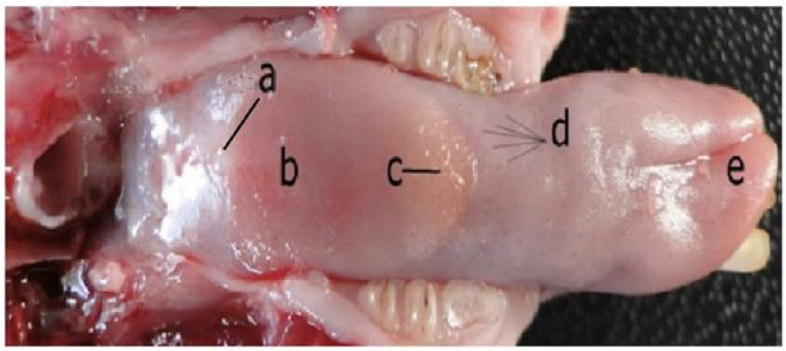

Figure 5: Tongue in rats (a: papilla vallata, b: radix linguae, c: papillae lentiformes, d: papillae fungiformes, e: apex linguae) (Anonymous 2)

Salivary glands (Glandulae salivaria)

In rats, there is thyroid gland (glandulae thyroidea), trachea and esophagus in the dorsal part of the neck, and a thick adipose tissue with thymus in the lower part (Anonymous 2).

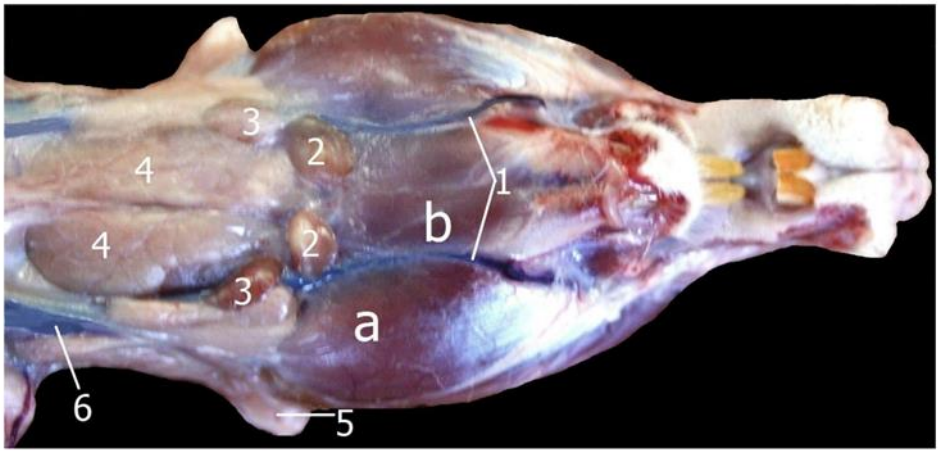

Figure 6: Ventral view of salivary glands in rats (1: facial vein, 2: mandibular rostral lymph node , 3: mandibular caudal lymph node, 4: mandibular glands, 5: parotid gland, 6: external jugular vein) (Anonymous 2)

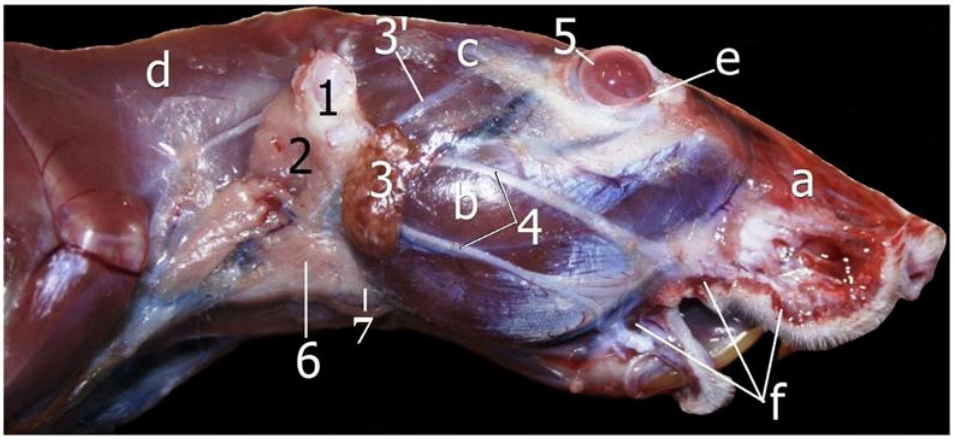

Figure 7: Lateral view of salivary glands in rats (1: Auricle, 2: parotid gland, 3: extraorbital lacrimal gland-l, 4: facial nerve, 5: Bulbus oculi, 6: mandibular gland, 7: sublingual gland) (Anonymous 2)

Pharynx

The pharynx covers a narrow area at the caudal of the oral cavity where the respiratory and digestive systems intersect (Gültiken 2010).

Esophagus

The esophagus is approximately 2 mm in diameter and lies slightly to the left of the median line in the cervical region. It has striated muscles along its entire length. Rats can't vomit either (Gültiken 2010).

Stomach (Gaster, ventriculus)

In rats, the stomach is located on the left side of the abdominal cavity, at the level of the last thoracal and first lumbar vertebra (Vdoviaková et al. 2016). Gaster is unicompartmented but shows two parts, glandular and cutaneous. Pylorus has a very muscular sphincter. Gaster is located to the left of the median line, above the hepar and caudal. It is attached to the hepar by the ligamentum gastrohepatica. The stomach lies caudoventral against the pancreas and colon. The spleen is next to the stomach. Rats do not have a gallbladder. They have a large caecum, and the digestion of cellulose takes place here. In the meantime, the synthesis of B vitamins takes place. (Gültiken 2010).

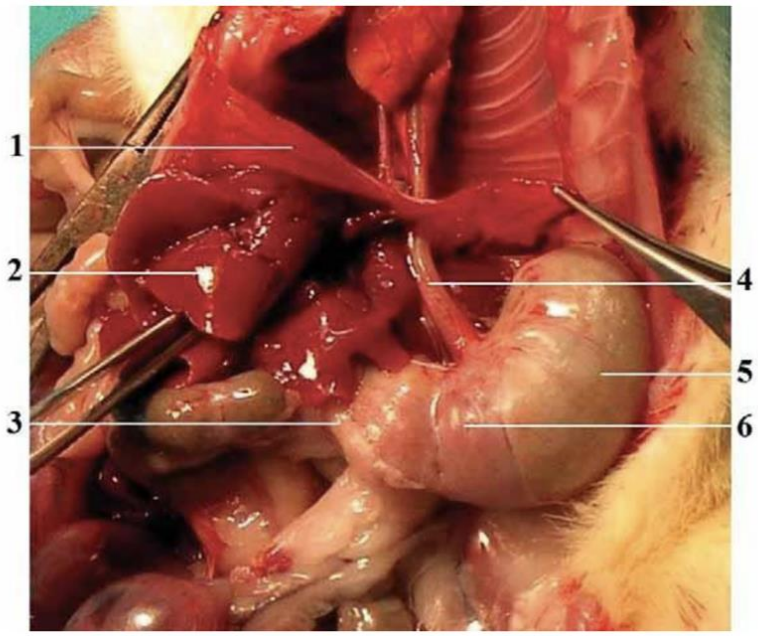

Figure 8: Some internal organs in rats (1: Diaphragma, 2: Hepar, 3: Duodenum, 4: Esophagus, 5: Stomach (pars non-glandularis), 6: Stomach (Pars glandularis)

Intestines (Intestinum)

Small intestines (Intestinum tenue)

The epithelial layer in the small intestines is completely renewed every five days. In other words, the surface of the small intestine five days ago and the surface of the present small intestine differ depending on the food taken (Karaismailoğlu 2019).

In one study, the total intestinal length in rats was reported to be 120-170 cm (Kararlı 1995). The small intestines are about 113 cm long (Gültiken 2010). It shapes the jejunum at its longest part (100 cm) and fills the right ventral part of the cavum abdominis (Gültiken 2010). In this animal species, a single biliopancreatic duct opens into the duodenum (Anonymous 2).

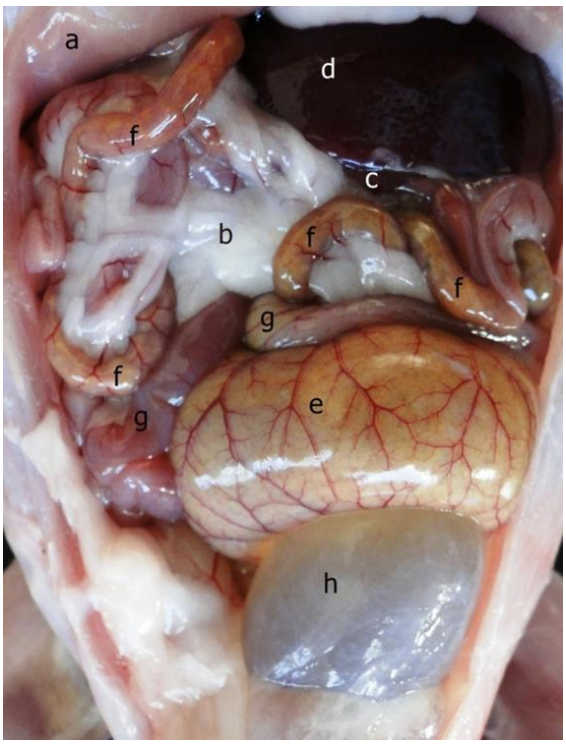

Figure 9: Ventral view of internal organs in rats (a: Diaphragma, b: Omentum, c: Stomach (Gaster), d: Liver (Hepar), e: Caecum, f: Jejunum, g: Colon, h: Bladder (Vesica urinaria)) (Anonymous 2)

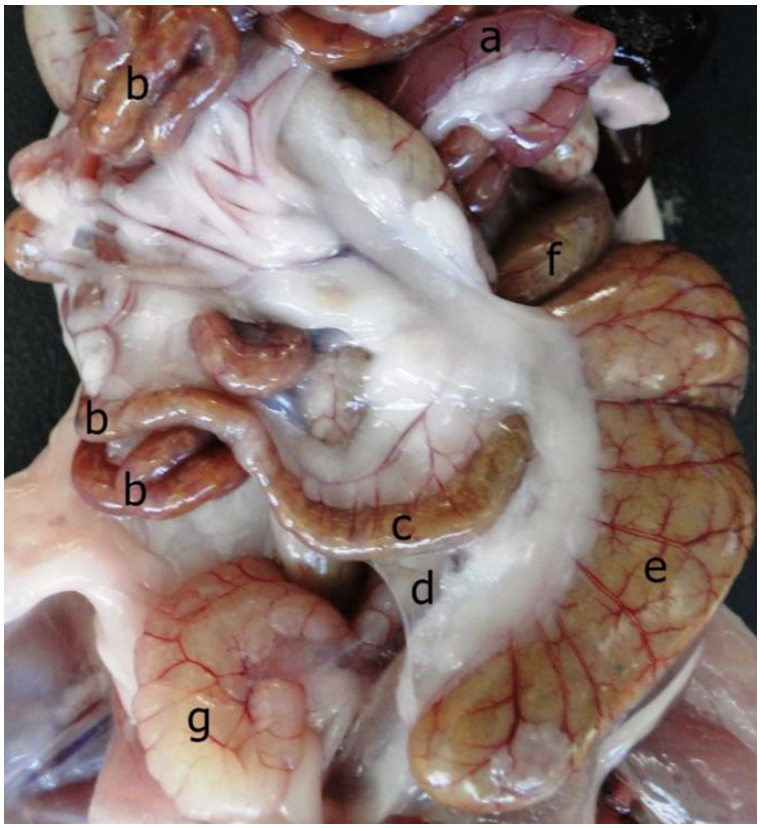

Figure 10: Intestinal sections in rats (a: Duodenum, b: Jejunum, c: Ileum, d: Ileocecal ligament, e: Caecum, f: Colon, g: Coagulation gland) (Anonymous 2)

Duodenum

The starting part of the duodenum is the pars cranialis duodeni. It is followed by the pars descendens duodeni. It then forms the fold called the flexura duodeni cranialis. It is followed by the pars ascendens duodeni. It ends by forming the flexura duodeni caudalis (Vdoviaková et al. 2016). The duodenum length in rats is 95-100 mm and the diameter is 2.5-3 mm (Kararlı 1995).

Jejunum

The jejunum length in rats was determined as 900-1350 mm and the diameter as 4-5 mm (Kararlı 1995).

Ileum

The length of the ileum in rats has been reported as 20-30 mm (Stable 1995). In the region where the ileum enters the caecum, there is a lymphatic organ called sacculus rotundus (Vdoviaková et al. 2016).

Large intestines (Intestinum crassum)

Although the colon is anatomically composed of the colon ascendens, the colon transversum, and the colon descendens, it functionally consists of two proximal and distal parts. The proximal colon is shorter (about 50 cm) and is characterized by three muscular bands called teniae, haustra, and fusus coli formed by these bands. There is no haustra in the longer (about 90 cm) distal colon. Fusus coli is a structure of 5-8 cm thick circular muscle covered with mucous membrane, unique to Lagomorphs. It has dense ganglion cells in its structure and these cells are under the influence of aldosterone and prostaglandins. These ganglion cells control the passage of intestinal contents into the distal colon by three types of colonic motility: segmental, peristaltic, and haustral. (Gültiken 2010).

Caecum

The comma-shaped caecum lies on the left side of the abdomen, its position may vary due to its long mesenterium. As with other rodents, it shows three parts: basis, corpus, and apex. The wall of the corpus ceci is thinner than other parts of the intestine, and the lymphoid tissue corresponding to the appendix is located near the apex (Gültiken 2010). The processus vermiformis extends from the apex of the caecum to the last part (Vdoviaková et al. 2016). The caecum length in rats has been reported to be 50-70 mm and a diameter of 10 mm (Kararlı 1995).

Colon

It is divided into three parts as colon ascendens, transversum, and descendens (Gültiken 2010). Colon length in rats was 90-110 mm and diameter was 10-13 mm (Kararlı 1995).

Rectum

The rectum is the continuation of the colon and ends with the anus. In the rectum epithelium, there are goblet cells that provide lubrication with their secretions to facilitate the outflow of stool (Gültiken 2010). It has been reported that the rectum length of rats is 80 mm and the diameter is 3-10 mm (Kararlı 1995).

Liver (Hepar)

The liver is located in the cranial of the cavum abdominis, leaning against the thorax. It consists of four lobes (lobus hebatis dexter lateralis and medialis, lobus medius and lobus hepatis sinister) (Gültiken 2010). However, in another study, it was reported that it consists of

six lobes in total (Vdoviaková et al. 2016). Its visceral surface is in contact with the stomach, duodenum descendens, colon transversum, jejunum, and spleen (Gültiken 2010).

Table 1. Liver lobes and gallbladder

	Lobus dexter	***Lobus sinister***	***Lobus intermedius***	**gallbladder**
RAT	***Single lobe***	***Lateral lob, Medial lob***	***Quadrat lob, Caudat lob (processus caudatus, processus papillaris)***	**note**

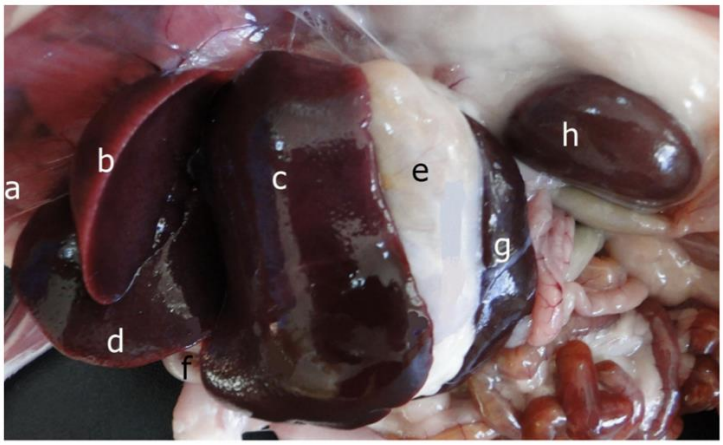

Figure 11: Liver lobes from the lateral in rats (a: Falciform ligament, b: Medial sinister hepatic lob, c: Lateral sinister hepatic lob, d: Dexter hepatic lob, e: Stomach, f: Duodenum, g: Spleen, h: Left kidney) (Anonymous 2)

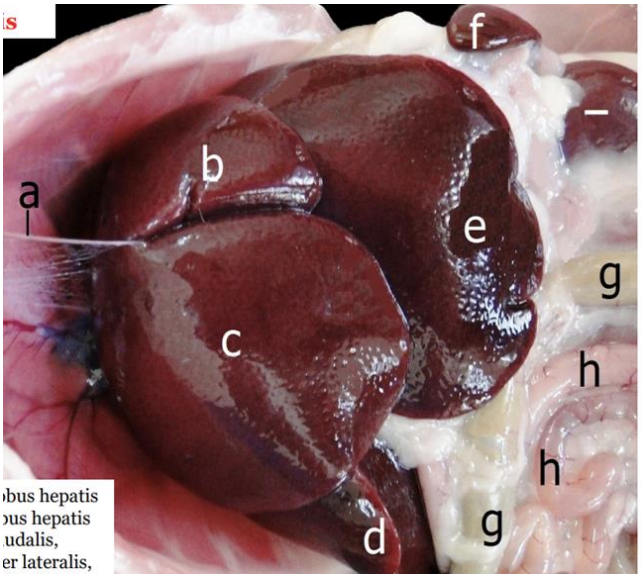

Figure 12: Liver lobes from ventral in rats (a: Falciform ligament, b: Medial sinister hepatic lob, c: Dexter hepatic lob, d: Processus caudalis, e: Lateral sinister hepatic lob, f: Spleen, g: Colon descendens, h: Jejenum, i: Right kidney) (Anonymous 2)

Gall bladder (Vesica fellea)

Rats do not have a gall bladder. Bile ducts unite to form the ductus hepaticus, which extends towards the pancreas. Bile and pancreatic secretion open with a common channel to the proximal part of the duodenum near the pylorus. (Gültiken 2010).

Pancreas

In rats, the pancreas is a whitish-gray, highly lobular, and diffuse organ. It can be distinguished from adipose tissue by its darker color and firmer consistency (Gültiken 2010).

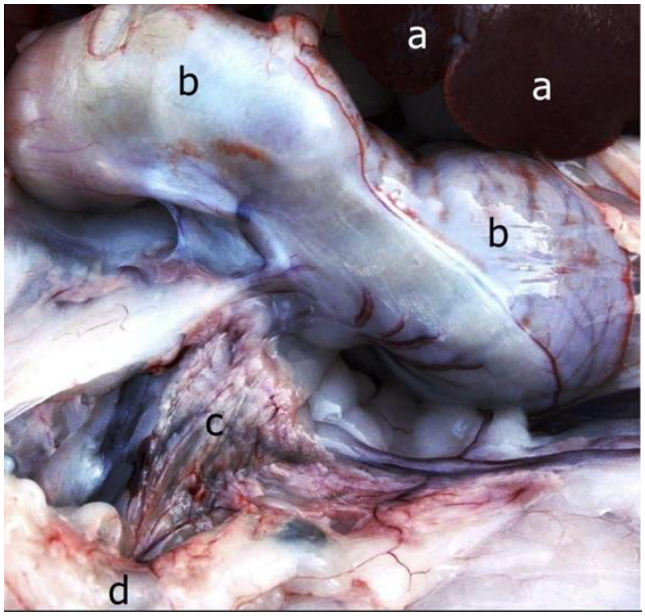

Figure 13: *Some internal organs in rats (a: Liver, b: Stomach, c: Pancreas, d: Duodenum) (Anonymous 2)*

Spleen (Lien)

The ratio of spleen to body weight remains fairly constant regardless of age and is typically around 0.2% in rats (Losco, 1992).

Anus

The skin around the anus is hairless and folded into the anus (fossa perinealis). There are many sebaceous glands in this area (coccigeal glands). The circumanal sebaceous glands are located in the perineal region. This is called the scrotal plug in the male. There are no sweat glands (Gültiken 2010).

Conclusion

It is thought that this study will support scientific studies on the digestive system in rats. Other laboratory animals can also be used in comparative studies.

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The Effects of Heat Stress on Rumen Microbiota and Feeding Strategies In Dairy Cattle

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Aslıhan SUR[2]

Introduction

Rising global temperatures pose a major problem for animal production. As ambient temperatures rise, the ability of animals to maintain thermal homeostasis through sensible (conduction, convection, and radiation) and latent (evaporation through sweating or respiration) heat loss declines. Cattle exposed to heat stress also have lower gross energy intake as dry matter consumption is reduced. Energy loss occurring through heat dissipation behaviours (rised respiration and heart rate) exacerbates the severity of energy need in cattle (Brown-Brandl, 2018; Koester & et al., 2022).

This reduction in net available energy means a drop in growth rate and milk yield (Gao & et al., 2017; Brown-Brandl, 2018; Menta & et al., 2022; Koester & et al., 2022). It has also been reported that chronic heat stress leads to delays in puberty and age at first calving in heifers and lower reproductive ability in cows, with an increased incidence of retained placenta and metritis (Menta & et al., 2022; Koester & et al., 2022).

The rumen microbial community has an important role in both animal health and performance as it ensures essential metabolic products for host animals through microbial fermentation of feeds (Xue & et al., 2020; Zhou, Ghoshal & Stothard, 2021; Koester & et al., 2022). Rumen microorganisms yield nutritionally valuable fermentation products such as short-chain fatty acids and vitamins through the destroy of cellulose, hemicellulose, and pectin (Averianova & et al., 2020; Beckett & et al., 2021; Koester & et al., 2022). These microbial metabolites produced in the rumen are directly absorbed by the host through the rumen epithelial tissue and utilised in the body. Rumen microorganisms are divided into three groups and they realize their functions: Microorganisms associated with the part of the rumen containing solid feeds, rumen fluid microorganisms, and rumen epithelial microbiota. The first two groups are collectively referred to as the rumen content microbiota (Zhou, Ghoshal & Stothard, 2021; Na & Guan, 2022; Koester & et al., 2022).

There is growing interest in how heat stress affects rumen microbial communities, and recent studies suggest that the rumen content microbiota is directly influenced by heat stress (Zhao & et al., 2019; Kim & et al., 2022; Wang & et al., 2022). However, none of these studies analysed rumen epithelial microbiota, and revealed the effects of heat stress on rumen epithelial microbiota. Heat stress results in negative consequences such as declined feed intake, rumen movement, and feed passage rate, which can affect the level of efficiency and reduce the substrate available for microbial organisms in the rumen. Furthermore, as a result of heat stress, alterations in host physiology can affect microbial population dynamics and metabolic

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outcomes in animals. These results are most pronounced in animals such as ruminants, where the microbiota is highly important. One way to improve the performance of cattle exposed to heat stress is to promote feed intake. Different flavour enhancers, including sodium-saccharin-based sweeteners, have been recommended to increase the feed intake of the animal, and such feed supplements are marketed for numerous animal species, such as pigs, sheep, and dairy cattle (Koester & et al., 2022).

Heat stress is reported to influence numerous metabolic processes in dairy cattle beyond declining feed intake. Levels of milk protein, lactose, and glucose, and circulating lipid levels have been reported to be lower in cattle exposed to heat stress (Wheelock & et al., 2010; Gao & et al., 2017). It is possible that some of these alterations may be partially correlated with changes in the microbial communities in the rumen during heat stress (Koester & et al., 2022). Zhao & et al., (2019) reported that the relatively abundance of *Spirochaeta, Streptococcus,* and *Ruminobacter* genera increased and acetic acid concentrations decreased in the rumen of lactating Holstein cows exposed to heat stress. Generally, studies have indicated that heat stress affects many metabolic processes in dairy cattle beyond reducing feed intake (Koester & et al., 2022).

Changes in the ration are necessary for hot weather to improve feed intake and the nutrient density of the ration or to restore homeostasis. The formulation for adequate nutrient intake remains challenging due to competition between nutrient density and other needs of the cow, including energy density and sufficient crude cellulose. Reduced dry matter consumption in hot weather also reduces absorption, and absorbed nutrients are utilised less efficiently. High levels of degradable protein in the ration require excess nitrogen to be metabolised and excreted as urea, which is not desirable as it causes additional energy losses. Optimising rumen undegradable protein in the rumen advances milk yield in hot climates. Mineral losses through sweating (primarily K) and changes in blood acid-base chemistry arising from hyperventilation lower blood bicarbonate levels, reduce blood buffering capacity and raise urinary excretion of electrolytes. In terms of theoretical heat production, concentrate feeds and fats lead to a lower heat rise, while roughages cause a higher heat rise (West, 1999).

Significance of Rumen Microbiota

Microbiomes affect almost all of the physiology of a living organism and represent one of the main factors in good health. The rumen of dairy cattle is a critical site for the metabolism and health of the host and contains an abundant and diverse range of microorganisms (Kim & et al., 2020; Kim & et al., 2022). The structure and functioning of the rumen microbiome are influenced by physical and chemical factors such as ration, feeding programmes, environmental conditions, feeding behaviours and individual characteristics (Kim & et al., 2022). Temperature, one of the environmental factors, can disrupt the interrelationships between animals and microbiomes through direct biological effects and ultimately affect animal welfare (Sepulveda & Moeller 2020; Kim & et al., 2022).

A ration is recognised as the main factor that affects rumen microbial fermentation. However, physiological alterations in host metabolism under heat stress may also cause changes in the rumen microbiota and affect nutrient absorption. Heat stress can lower reproductive performance and productivity level due to reduced dry matter consumption, decreased rumen motility and contraction, and altered fermentation during fatty acid formation. All these alterations can influence the digestion and utilisation of nutrients (Correira & et al., 2021).

Animals demonstrate various physiological, endocrinological, and behavioural mechanisms to combat heat stress. Generally, the drop in feed intake due to heat stress is considered to be the main underlying cause of negative energy balance and reduced milk yield (Sammad & et al., 2020; Kim & et al., 2022). Dairy cattle exposed to heat stress may face the

risk of rumen acidosis (Sammad & et al., 2020; Kim & et al., 2022) when pH levels fall (Kim & et al., 2022) due to elevated lactic acid concentrations.

Low pH levels cause fibrinolytic bacteria to decline and cellulose digestibility to fall (Baek & et al., 2020; Kim & et al., 2022). Excessive consumption of concentrate feed rather than roughage reduces rumination and rumen motility, which reduces saliva production, a buffering agent in the rumen, and thus rumen pH may fall (Kim & et al., 2022). Consequently, an elevated level of lactate-producing bacteria and a drop in acetate-producing bacterial species in the gut microbial community are reported as potential causes of declined milk production (Zhao & et al., 2019).

Physiological and metabolic alterations caused by heat stress are reported as changes in immune functions, increased expression of heat shock proteins, elevated body temperature, respiratory rate, non-esterified fatty acids, blood urea nitrogen, and ketone bodies, and reduced feed intake, blood glucose, cholesterol, and mineral concentrations (Sammad & et al., 2020; Yue & et al., 2020; Kim & et al., 2022).

Effects of Heat Stress on Rumen and Rumen Microbiota

The appetite centre in the hypothalamus is negatively influenced by changes in ambient temperature, and feed intake may be observed to reduce. The feed intake in lactating cows begins to reduce when the ambient temperature is 25–26 °C, and a rapid decline is observed when the ambient temperature rises above 30 °C. In ruminant animals, feed intake generates a significant amount of heat. Therefore, reduced feed intake may help reducing heat generation in hot conditions (Kim & et al., 2022). This leads to a negative energy balance by lowering live weight and body condition scores (Das & et al., 2016; Kim & et al., 2022). High ambient temperatures, which negatively affect ruminants, change the basic physiological mechanism of the rumen and may lead to health problems. It is also highly risky for metabolic diseases (Kim & et al., 2022). Heat stress can adversely affect energy metabolism and lower metabolic heat generation, both of which are required to maintain a normal body temperature (Kang & et al., 2019; Kim & et al., 2022). It can also reduce rumination, rumen activity, and reticulo-rumen motility, which in turn can affect the fractional passage rate of the digestive tract in the gastrointestinal tract (Kim & et al., 2022).

Stress factors negatively affect rumen fermentation and the development of rumen microorganisms (Yu & et al., 2020). Heat stress significantly reduces most species of rumen microorganisms, such as *Methanobacteria, R. albus, F. succinogenes,* and fungi (Yu & et al., 2020). High rumen temperatures can alter the rumen microbial population (Figure 1). Relatively abundance of *Fibrobacter succinogenes, Flavonifractor, Prevotella ruminicola, Ruminococcus flavefaciens,* and *Treponema* bacteria in the rumen may decline. A decline of these bacteria in the rumen increases the lactic acid bacteria population since an amount of substrate suitable for their metabolism is provided (Correira & et al., 2021).

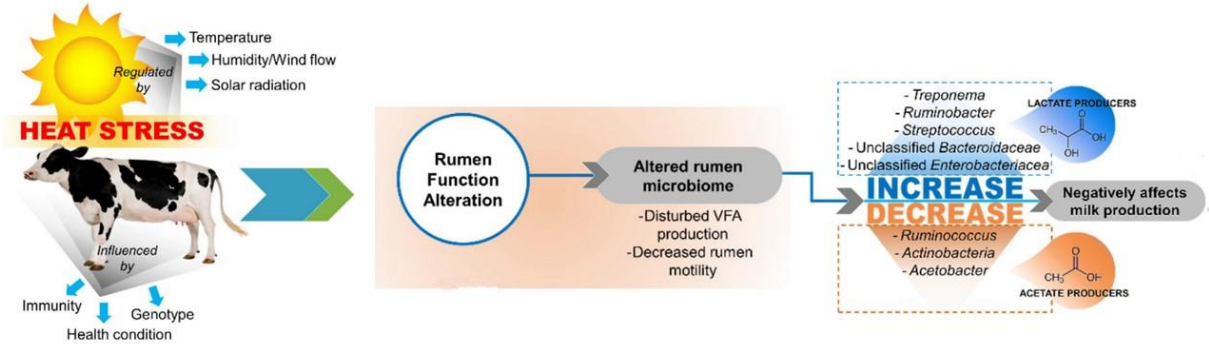

Figure 1. Effect of heat stress on the rumen microbiome and milk production mechanisms

Heat stress affects the rumen microbiome of lactating cows (Kim & et al., 2020; Kim & et al., 2022). It has been reported that heat stress significantly increases soluble carbohydrate-utilizing bacteria such as *Streptococcus*, unclassified *Enterobacteriaceae, Ruminobacter, Treponema*, and unclassified *Bacteroidaceae* (Zhao & et al., 2019). The major genus of lactate-producing bacteria in the rumen is *Streptococcus* (Calsamiglia & et al., 2012). Also, the majority of *Enterobacteriaceae* (Zhao & et al., 2019) also produce lactate; therefore, they are potentially the precursors to elevating lactate concentration and lowering rumen pH. The rise in lactate levels and fall in pH in the rumen appear to be accompanied by an increase in relatively abundance of *Streptococcus* (Kim & et al., 2022). Therefore, it is reported that the elevated lactate production in the rumen during heat stress results from a proliferation in lactate-producing bacteria (e.g., *Streptococcus*) (Zhao & et al., 2019).

Treponemas are primarily involved in the breakdown of pectin and also take part in the digestion of concentrate feeds. Additionally, *Ruminobacter amylophilus* (a representative species of *Ruminobacter*) shows a high ability to degrade starch in the rumen (Kim & et al., 2022). For this reason, the elevated number of bacteria that produce lactate or digest soluble carbohydrates in dairy cattle under heat stress may be based on the higher ratio of concentrate feed to roughage in the ration (Zhao & et al., 2019). Also, heat stress may decline relatively abundance of *the Acetobacter* that produces acetate by oxidising sugars. The decline in *Acetobacter* is consistent with the decline in acetate in rumen fluid (Zhao & et al., 2019).

Heat stress can also alter rumen microbiota and fermentation in heifers. Under heat stress, the rumen microbiota community is significantly restructured by changes in the composition and volume of feed, causing to changes in the rumen fermentation product (Wang & et al., 2020). Uyeno & et al., (2010) reported that the group of *Clostridium coccoides-Eubacterium rectale*, a cluster of butyrate-producing bacteria, and the genus *Streptococcus* proliferated, while the genus *Fibrobacter*, a representative of acetate-producing bacteria, declined in heat-stressed heifers (33°C). Also, some studies have reported that the concentration and content of acetic acid declined and concentration and content of acetic butyric acid rose in heifers under heat stress conditions (approximately 32 to 33 °C ambient) (Wang & et al., 2020). These changes in heat stress may negatively affect the growth performance of the growing cattle due to the lower amounts of volatile fatty acids, which are primarily used as energy sources (Tajima & et al., 2007; Wang & et al., 2020).

In a study conducted by Wang et al., (2022) to investigate the effects of different heat resistances using rumen bacteria and metabolome analyses in Holstein cows, they reported that the relatively abundances of *Muribaculaceae, Rikenellaceae, Acidaminococcaceae, Christensenellaceae, Rikenellaceae RC9* gut_group, *Succiniclasticum, Ruminococcaceae* NK4A214 group, and *Christensenellaceae* R-7 group significantly increased in heat-tolerant cows compared to heat-sensitive cows. A study reported that *Ruminococcaceae*_UCG-014, *Ruminococcaceae* NK4A214 group, and *Rikenellaceae* group bacteria were correlated with feed intake behaviours in animals (Bainbridge & et al., 2016; Zhao & et al., 2017). *Rikenellaceae* were able to degrade structural carbohydrates and starch in the rumen of dairy cattle (Ametaj & et al., 2010). Furthermore, substances involved in carbohydrate metabolism, including glycerol, mannitol, and maltose, were reported to be significantly higher in heat-tolerant cattle compared to heat-sensitive cattle, suggesting that such substances may be correlated with better adaptability to heat stress (Wang & et al., 2022).

The analyses of bacterial composition in the rumen of Holstein cattle using 16S rRNA amplicon sequences revealed that the relatively abundance of the *Fibrobacteraceae* family, especially the members of the phylum *Fibrobacteres*, significantly increased under heat stress. A possible reason for this was reported to be due to the higher resistance of *Fibrobacteres* and their families under the *Fibrobacterales* group to heat compared to other ruminal bacteria (Kim

& et al., 2020). This group may be correlated with the cellulolytic activity prevalent in ruminal microorganisms (Puniya, Singh & Kamra, 2015; Kim & et al., 2022). The microbial metabolic activity of the rumen may be directly correlated with heat generation in the rumen, which can be predicted indirectly through bacterial growth activity (Kim & et al., 2020). Generally, microorganisms may be endowed with unique mechanisms for responding to heat stress, such as adaptation to a given temperature and resistance to higher temperatures (Kim & et al., 2022).

Some Nutritional Strategies for the Recovery of Rumen Microbiota in Dairy Cattle Under Heat Stress

Heat stress negatively influences ruminal bacterial composition and metabolism, which results in more lactate and less acetate production by the bacteria and may adversely affect cattle health or milk production. It has been reported that nutrients or supplements should be used to regulate rumen microbial fermentation to reduce the negative effects of heat stress (Zhao & et al., 2019). The studies have tried to regulate rumen fermentation with the use of different supplements, and therefore, it would be possible to improve strategies to eliminate the negative effects of heat stress on rumen microbiota with the support of the literature.

In lactating cattle, heat stress is reported to influence the structure of three different orders in the rumen microbiota: prokaryotes, fungi, and protozoa. Heat stress acts selectively on some taxa of bacteria, fungi, and protozoa while diminishing others. The ratio of *Firmicutes* to *Bacteroidetes* and many genera (*Ruminococcus, Desulfovibrio, Piromyces*, and *Isotricha*) may either fall or rise (*Anaeroplasma, Shuttleworthia,* and *Filobasidium*) in cows exposed to heat stress. Some bacteria that are resistant to heat stress and fungi may be benefical as potential probiotics for cows under heat stress (Park & et al., 2022).

Rumen fermentation and microbial community are reported to be modulated by raising the anion-cation difference of the ration in Holstein dairy cattle exposed to heat stress. Wang & et al., (2021) divided 8 lactating cows into two groups with normal (Control: 33.5 mEq/100 g dry matter) and high (50.8 mEq/100 g dry matter) ration anion-cation differences and collected and analysed rumen fluid on the 15th and 21st days of each 21-day period. The absolute concentration of total volatile fatty acid in the ruminal fluid was found to be significantly ($P < 0.05$) higher in the group with a higher difference compared to the control group. Also, the replicate members of *Ruminococcus albus* and *Ruminococcus flavefaciens* cellulolytic bacteria in the ruminal fluid proliferated together in the group where the anion-cation difference was raised. Although alpha diversity indices and bacterial microbiota structure were not affected, the elevated anion-cation difference significantly ($P<0.05$) enriched the genus *Fibrobacter* of the phylum *Fibrobacteres* in the rumen fluid microflora; whereas, *Flexilinea* and *Dubosiella* genera were the most abundant in the control group. Consequently, despite the observation that some cellulolytic/hemicellulosic bacteria were enriched with the rise in ration anion-cation difference in heat stress, it was reported that a higher total UYA concentration appeared without affecting rumen bacterial diversity or structure.

One way to prevent a decline in performance under heat stress is reported to be to promote feed intake. Saccharin-based sweeteners may have a positive effect on cattle that struggle with these stressors (Koester & et al., 2022). Koester et al., (2022) studied the influence of a saccharin-based artificial sweetener on performance, rumen content, and microbial communities associated with rumen epithelium in heat-stressed animals and supplemented 10 cannulated Holstein-Friesian dairy cows with 2 g of saccharin-based sweetener per day. After an adaptation period of 7 days, they imposed heat stress for 14 days. For comparison, they included a control group including 10 additional cows that were subjected to the same ambient conditions but fed a diet without sweetener supplementation. They sequenced 16S rRNA gene amplicons in rumen content and rumen epithelium specimens from all animals and compared

rumen content microbiota and rumen epithelium microbiota between control and heat stress groups. They reported that the saccharin-based sweetener supplements showed no effect on rumen content microbiota, but differences were identified in rumen epithelial microbiota beta diversity and alpha diversity between the groups. In spite of the changes identified in the microbial community, they reported that animal performance evaluations, including feed intake, milk yield, and short-chain fatty acid (acetic, propionic, and butyric acid) concentrations, did not differ among the experimental groups. They also reported that there were differences in rumen epithelial microbiota when comparing microbial communities before and after stress. In conclusion, they reported that the sweetener induced changes in rumen microbial communities, especially in microbial communities attached to the rumen wall, and these changes in rumen wall microbial communities may have potential implications for the host animal, such as the integrity of the rumen wall barrier function.

Betaine (trimethylglycine) has numerous functions in lactating dairy cattle that may alleviate the effects of heat stress and increase milk production. For instance, betaine (Bet) is an osmolyte and a methyl donor. It acts as a molecular chaperone, reduces the vulnerability of microorganisms to stress, and exhibits antimicrobial activity under certain conditions. Betaine is not also an amino acid but also has the ability to advance the production performance of different animals, such as cattle and pigs. These outcomes comments that betaine can potentially alleviate heat stress by lowering energy consumption, thus reducing metabolic heat production and maintaining osmotic balance in animals exposed to heat stress (Shah & et al., 2020). Shah & et al., (2020) examined the influence of betaine on productivity, performance, rumen fermentation, and antioxidant profile by adding betaine to the rations of dairy cattle. They reported that the concentrations of volatile fatty acids, acetate, and propionate increased with betaine supplementation, and therefore it is possible that betaine supplementation may improve rumen fermentation by serving as a source of available nitrogen or methyl groups in the rumen. Wdowiak-Wróbel, Leszcz & Malek, (2013) suggested that betaine addition exerts an osmoprotective effect and supports favourable microbiota growth in the rumen under environmental stress conditions. Reportedly, betaine is metabolised in the rumen and turned into acetate, which can have a major role in fat synthesis (Peterson & et al., 2012).

In animals exposed to heat stress, yeast supplementation may have positive effects on the microbiota and fermentation in the rumen and intestines. Li & et al., (2023) studied the effects of live yeast (*Saccharomyces cerevisiae*) on lactation performance, and bacterial community, and functions of the rumen and large intestine in dairy cattle exposed to heat stress. They randomly divided thirty-three multiparous Holstein dairy cattle into three groups and fed a ration containing no yeast supplementation, 10 g yeast/day/head and 20 g yeast/day/head. They reported that yeast supplementation lowered the rectal temperature and respiratory rate of cows and increased dry matter consumption, milk yield, milk fat, milk protein, and milk lactose levels. It was reported to raise the concentrations of acetate, isobutyrate, isovalerate, valerate, total volatile fatty acids, and NH3-N in rumen fluid. Miseq sequences of 16S rRNA genes showed that yeast supplementation increased the relative abundance of *Prevotella* and *Prevotellaceae* UCG-003 in rumen fluid, and analysis of faecal samples noticed that the abundance of *Clostridium sensu stricto* 1 and *Actinobacillus* increased by yeast, while the abundance of *Bacteroides* and *Oscillospirales* UCG-010 declined. Yeast supplementation was reported to have a positive effect on rumen and intestinal health and reduce the harmful effects of heat stress on dairy cattle (Li & et al., 2023).

Zhuang & et al., (2021) assessed the physiological index, growth performance, and faecal microbiota of cattle in their research on the influence of fermented herbal tea wastes on heat stress in cattle. They reported that fermented herbal tea wastes effectively lowered the respiratory rate and rectal temperature of cattle under heat stress, can increase daily feed intake

and daily gain, and enhance antioxidant status. They also stated that the nutrient significantly altered faecal microbiota composition and promoted microbial diversity. They reported that the abundance level of *Firmicutes* in the group given fermented herbal tea wastes was significantly higher, and Bacteroidetes levels were significantly lower than in the control group. It is noticed that *Bacteroidetes* are primarily responsible for the breakdown of the fibrous structure, are associated with rations with high cellulose content, and also proliferate under heat stress (Zhuang & et al., 2021; Zhao & et al., 2019). According to the study, it is possible to conclude that the addition of fermented herbal tea wastes to the ration has an effect on lowering the level of Bacteroidetes under heat stress. In another study, the researchers analysed the influences of fermented herbal tea residues on the intestinal microbiota characteristics of Holstein heifers under heat stress (Xie & et al., 2020). The findings reporting that the addition of fermented products to the ration contributed to the improvement of physiological indices of respiratory frequency and rectal temperature and the rise in parameters related to antioxidant capacity suggested that heat stress may be advantageous for dairy cattle.

Dihydropyridine (DHP) is a Ca^{2+} channel antagonist that can inhibit Ca^{2+} influx into the cytoplasm and lower cytoplasmic Ca^{2+} concentration (Yu & et al., 2020). DHP is generally used as a therapeutic agent for diseases such as myocardial ischaemia (Liyang & et al., 2006; Yu & et al., 2020), hypertension (Wang & et al., 2011; Yu & et al., 2020) and kidney (Robles & et al., 2016; Yu & et al., 2020) diseases. Also, DHP is used as a supplement in animal rations because of its antioxidant (Wu, 2020) properties that protect fat, vitamin A, and beta-carotene against oxidation. It has been reported that these properties make DHP a potential candidate for a good feed supplement to reduce the detrimental effects induced by heat stress (Yu & et al., 2020). A study examined the effects of DHP on the alteration in the structure and composition of rumen microbes (bacteria, protozoa, archaea, and fungi) in lactating dairy cows. A total of 20 cows were randomly divided into a control group and an experimental group (n = 10) to analyse the effects of DHP on antioxidant status and ruminal microorganisms in dairy cows in the mid-lactation. The cows in the control group were fed a basal ration, while the cows in the experimental group were fed a ration containing 3 g/day/cow DHP. DHP was first mixed with a small amount of concentrate feed and then with all other feeds. For the analysis of rumen microorganism composition, rumen fluids were collected and stored at -20 °C. In conclusion, the supplementation of DHP could reverse the decline in rumen microorganisms, indicating that DHP can alter the structure and composition of rumen bacteria in dairy cattle. Also, relatively abundance of the *Methanobacteria* unexpectedly declined after the supplementation of DHP, and it was reported that this may be because of the depletion of two types of materials (acetic acid and hydrogen) that synthesise methane. Acetic acid content declined under heat stress conditions. DHP increased hydrogen-related microorganisms such as *B. fibrisolvens* and *C. proteoclasticum*, consuming a lot of hydrogen. For this reason, the growth of *Methanobacteria* was inhibited, causing to a decline in methane production. Based on these results, it was suggested that DHP may significantly change the structure and composition of rumen microbes and consequently affect the fermentation in the rumen of dairy cows. Phylogenetic analyses of rumen bacteria have reported that most of rumen bacteria belong to *Proteobacteria* and *Firmicutes*. DHP can increase the diversity of rumen bacteria. In particular, it can support the growth of *Xanthomonadaceae* and *Xanthomonas* bacteria. Briefly, the supplementation of DHP to the ration was found to be beneficial in improving the ruminal microorganism biodiversity of dairy cattle under heat stress. These beneficial effects may facilitate the enhancement of milk yield by improving the health of dairy cows, and DHP supplements may benefit the dairy cow industry as a benefical way to relieve dairy cows from heat stress (Yu & et al., 2020).

Consequently, microorganisms, which are highly abundant in the rumen of dairy cattle, can serve a pivotal role in the basic digestive and metabolic processes in the rumen. Heat stress

would affect the rumen microbiota in cattle, as temperatures rise, especially on a global scale. These problems and the possibility of a food crisis as the world's population grows necessitate the correct feeding strategies for cattle. It is believed that innovative studies on feeding strategies would be beneficial in eliminating the negative effects of heat stress in cattle.

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Chylothorax: Dıagnosıs And Treatment Optıons

Murat SARIÇAM[1]

Introduction

Chylothorax is the accumulation of chyle in the thoracic cavity developing due to the leakage of lipd-rich chyle as a result of structural damage in the thoracic duct (Rudrappa & Paul, 2023). Development of non-traumatic chylothorax is relevant to a wide range of medical disorders while traumatic causes mostly include injuries of the chest and post-surgical complications (McGrath, Blades & Anderson, 2009).

Anatomy

Small- and medium-chained triglycerides are digested into free fatty acids by the intestinal lipases and then transferred into the portal circulation. The long-chain triglycerides unite with phospholipids, cholesterol and cholesterol esters to compose chylomicrons which are absorbed by the small intestine. Finally, lymphatic vessels transport the chyle into the bloodstream via the thoracic duct.

The thoracic duct originates from the abdomen at the cisterna chyli and ascends through the posterior mediastinum between the azygous vein, the descending thoracic aorta, and the esophagus. The thoracic duct then crosses to the left of the esophagus, moves up posterior to the aortic arch ends after joining the left jugular vein (Riley & Ataya, 2019). Although his description is mostly valid for the majority of population, potential anatomical variations provoke challenges with diagnosis and treatment of the disease. Its course also respresents the side of development for chylous effusions based on the level of the thoracic duct damage. Chylothoraces are 50% right sided, 33.3% left sided and bilateral in 16.66% of cases (Rehman & Sivakumar, 2022).

Aetiology

Chylothorax is a rare condition counting up to 3% of all pleural effusion cases. Traumatic account up to 50% of chylous effusions and may be divided into groups as surgical and nonsurgical aetiologie. The two most common surgical causes leading to a chylothorax are esophagectomy and surgeries for congenital heart diseases. Non-surgical trauma to the chest or increased intra-abdominal pressures such as blunt trauma, childbirth, stretching, sneezing, vomiting,or seat belts may also lead to a chylothorax (Rudrappa & Paul, 2023).

The leading cause of a non-traumatic chylothorax is malignancy, including almost a third of all cases. Lymphoma is responsible for 70–75% of cases of malignant chylothorax as non-Hodgkin lymphoma appears as the most prevalent factor (Rehman & Sivakumar, 2022). The causes of non-traumatic chylothorax are listed in Table 1.

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Table 1. Causes of Non-traumatic Chylothorax

	Diseases
Malignancy	Lymphoma, esophageal carcinoma
Congenital Disorders nail	Congenital thoracic duct absence or atresia, yellow syndrome, lymphangioleiomyomatosis (LAM)
Infections	Histoplasmosis, tuberculosis
Systemic Disorders sarcoidosis	Behçet's disease, systemic lupus erythematosus,
Others	Idiopathic, congestive heart failure, superior vena cava thrombosis, enlarged mediastinal lymph nodes

Diagnosis

Patients with chylothorax are freqeuntly presented with dispnea, coughing and chest pain. Chest X-ray or computed tomography reveal pleural effusion which may appear at variable amounts. Besides, applying convenient imaging methods is effective in clarifying the cause of a malignant chylothorax or administrating an appropriate follow-up strategy for the treatment .

A pleural effusion is primarily suspected to be a chylothorax when the fluid obtained via thoracentesis demonstrates a milky color. Analysis of the fluid reveals triglyceride count more than 110 mg/dL whereas ratio of triglyceride over cholesterol counts is greater than 1. Proving the presence of chylomicrons in the fluid is accepted to be the gold diagnostic standard while cell count of the effusion revealing >70% lymphocytes support the evidence (Nadolski, 2016).

Pseudochylothorax develops when an exudative effusion following events such as tuberculous pleurisy, chronic pneumothorax, rheumatoid pleurisy, poorly evacuated empyema and chronic haemothorax remains in the pleural space for a long period of time (McGrath, Blades & Anderson, 2009). Differentiation between pseudochylothorax and chylothorax can be achieved by using the criteria listed in Table 2.

Table 2. Specifications of Pleural Fluid for Pseudochylothorax and Chylothorax

	Triglyceride	Cholesterol	Chylomicrons	Cholesterol crystals
Chylothorax	> 110 mg/dl	< 200 mg/dl	Present	Not seen
Pseudochylothorax	< 110 mg/dl	> 200 mg/dl	Absent	Often seen

Treatment

Traiditionally, both traumatic and nontraumatic chylothoraces are initially treated conservatively by nil per os, parenteral nutrion and low fat diets. Thereafter, patients who have

failed conservative treatment recieve thoracentesis, pleural drainage and pleurodesis (Kerlan & Laberge, 2012).

Considering the high rate of anatomic and aetiological variabilities within nontraumatic chylothorax, preinterventional imaging is crucial to assess the underlying lymphatic pathology as well as the possible leakage site. For this reason, MR lymphangiography is performed to investigate any leakage from the thoracic duct, abnormal pulmonary lymphatic flow, lymphatic flow from the abdomen into the chest or lymphatic masses in the retroperitoneum (Nadolski, 2016).

Various drugs including etilefrine, somatostatin and octreotide have been reported to introduce supplementary effect during conservative treatment. Etilefrine decreases the output of chyle by contracting the thoracic or main lymphatic ducts through its sympathomimetic effect. Both somatostatin and, its analog octreotide which has superior selectivity and longer half-life, reduce lymphatic flow by incresing the resistance to splenic blood flow (Esme, 2019).

Thoracic duct embolisation and surgical procedures such as mass ligation through open thoracotomy or thoracoscopy are generally advised after two weeks of conservative management. The likelihood of successful conservative treatment is reduced when the when the amount of chylous drainage exceeds 1000 ml/day for >5 days or 1500 ml/day in an adult patient (Nair, Petko & Hayward, 2007).

Percutaneous embolization of the cisterna chyli or the thoracic duct by interventional radiography is a minimal invasive interventional alternative to surgical treatment. Direct wound ligature or en masse supradiaphragmatic ligature are presented as preferred surgical techniques while pre-operative enteral administration of methylene blue or lymphangiography may help to identify the site of leakage (Meguid, 2016). Other methods including pleuroperitoneal shunt, pleurectomy, pleurodesis, or radiotherapy are rarely indicated in non-traumatic cases (Bryant & ark., 2014).

Conclusions

Chylothorax developing due to a vast number of traumatic and non-traumatic causes may lead to elevated rates of morbidity and mortality. It presents radiological findings as any other pleural effusions whereas the diagnosis can be finalised via the examination of the pleural fluid. Treatment strategy starts with conservative approach such as nil per os and parenteral nutrion followed by pleural drainage, thoracic duct embolisation or surgical interventions if not succeeded.

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Overview of the Management of Membranous Nephropathy in the Light of Current Guidelines

Mustafa TOPAL[1]

Introduction:

Membranous nephropathy is one of the most common causes of nephrotic syndrome in adults. The term 'mebranous' reflects glomerular basement membrane thickening along with subepithelial immune-complex deposits in histopathological examination. Membranous nephropathy accounts for 20 to 30% of nephrotic syndrome in white non-diabetic adults (Debiec & Ronco, 2014; Cattran & Brenchley, 2017) and has an incidence of 1/100000 annually (Alsharhan & Beck 2021). It is commonly detected over 40 years of age with a male predominancy (Ronco et al,2021; Turkmen et al, 2020). 75-80% of patients are classified as primary membranous nephropathy (Couser, 2017). The rest 20-25% is defined as secondary which may be associated with various disorders like malignancies, autoimmune or infectious diseases (table 1).

Approximately 80% of patients present with nephrotic syndrome whereas the majority of remainders are diagnosed as asymptomatic proteinuria. Proteinuria may range from subnephrotic to more than 20 g/day. Although microscopic hematuria may accompany in up to 50% of cases, casts are rarely seen (Wasserstein, 1997). Hyperlipidemia and hypercoagulability are frequently seen in patients with nephrotic syndrome. Hypertension is not a common finding, 30% of patients may experience elevated blood pressure (Beck & Salant, 2023a).

Pathogenesis and serologic markers:

Membranous nephropathy is an autoimmune mediated disease. Auto-antibodies against podocyte components leads to damage in podocytes whether complement-dependent or not. The main autoantibodies against podocyte components are anti-M type phospholipase A2 receptor 1 antibody (anti-PLA2R), anti-thrombospondin type 1 domain-containing 7A antibody (anti-THSD7A), anti-neural epidermal growth factor-like 1 (anti-NELL-1), anti-semaphorin 3B, anti-exostin 1 and 2 and protocadherin 7 (anti-PCDH7) (Beck & Salant, 2023b). Patients who have membranous nephropathy with anti-NELL-1 and anti-THSD7A antibodies should be carefully evaluated because they are more likely to have malignancy (Caza et al, 2021; Hoxha et al, 2017). Especially the description of anti-PLA2R antibody in 2009 helped a better understanding in membranous nephropathy pathogenesis (Beck et al, 2009). This antibody targets the N-terminal cystein-rich region of the PLA2R protein (Fresquet et al, 2015; Kao et al, 2015; Beck, 2015). Anti-PLA2R antibody was shown to have 78% sensitivity and 99% specifity for the diagnosis of membranous nephropathy (Du et al, 2014). Anti-PLA2R antibody is found to be positive in 60-70% of all membranous nephropathy cases, and up to 80% of primary membranous nephropathy (Debiec & Ronco, 2011; Qin et al, 2011; Hofstra et al, 2011; Hofstra et al, 2012; Kanigicherla et al, 2013; Ruggenenti et al, 2015). Higher anti-PLA2R levels are associated with poor response to immunosuppressive therapy, poor kidney survival,

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treatment relapses and relapse after kidney transplantation (Wiech, Stahl & Hoxha, 2019; Hoxha et al, 2014; Pang et al, 2017; Stai et al, 2023; Özer et al, 2023). Patients with positive antibodies, are also less likely to experience a remission whether spontaneous or with immunosuppressive therapy. For this reason, in updated guidelines released in 2021 by Kidney Disease: Improving Global Outcome (KDIGO), anti-PLA2R antibody was recommended to be used in diagnosis, disease activity, prognosis, therapeutic strategy and follow up (Rovin et al, 2021; Stai et al, 2023).

Table 1: Secondary causes of membranous nephropathy.

Neoplastic diseases: *Carcinomas (lung, prostate, breast, stomach, colon, renal cell)* *Lymphoproliferative (non-Hodgkin's lymphoma, chronic lymphocytic leukemia)*
Infections: *Hepatitis B virüs* *Hepatitis C virüs* *Human immundeficiency virüs* *Syphilis*
Systemic lupus erythematosus (WHO class V lupus nephritis)
Other immune diseases (rheumatoid arthritis, Hashimato's thyroiditis)
Drugs: *Nonsteroidal antiinflammatory drugs* *Anti-TNF treatment* *Gold* *Penicillamine* *Mercury* *Formaldehyde* *Probenecide*
Sickle cell anemia
Sarcoidosis
Post-transplantation de novo disease due to donor-specific anti-HLA antibodies
Hematopoietic cell transplant/ graft versus host disease

Pathology:

Histopathologic findings are characteristic in membranous nephropathy. In early stages, light microscopy may not be helpful. As the disease progresses, diffuse thickening of glomerular basement membrane becomes apparent. In more advanced disease, the matrix deposition will result in spike-like projections and further in lace-like splitting in glomerular basement membrane (Beck & Salant, 2023a). On immunofluorescence microscopy examining, diffuse granular staining of IgG and C3 is revealed along glomerular basement membrane, as well as PLA2R and THSD7A. Immunofluorescence microscopy is usefull in early stages for detecting deposits. On electron microscopy, foot process effacement with electron-dense deposits in the outer part of glomerular basement membrane leading to expansion of glomerular basement membrane is characteristic.

Renal biopsy:

While renal biopsy was a necessity for diagnosis before, it is not required in some selected cases with the new guidelines. In individuals who have positive anti-PLA2R antibodies with typical nephrotic syndrome and no unusual immune profile or declining renal functions, treatment may be started without performing a renal biopsy (Rovin et al, 2021). Patients with rapidly declining renal functions, lack of response to therapy or persisting nephrotic syndrome despite the disappearing of anti-PLA2R antibody should undergo a renal biopsy.

Decision of treatment:

Despite 30-35% of patients will experience spontaneous remission in the first year, nearly the same amount will develop renal failure in ten years (Hogan et al, 1995; Schieppati et al, 1993; Ponticelli et al, 1995; Jha et al, 2007; Segal & Choi, 2012). While spontane remission is common, risk groups were defined in new guidelines for starting treatment and follow-up (Rovin et al, 2021). These are low (normal eGFR, proteinuria <3.5 g/d and serum albumin >3 g/dl or a decrease of %50 in proteinuria after 6 months of conservative therapy), moderate (normal eGFR, proteinuria >3.5 g/d, less than %50 reduction in proteinuria after 6 months of conservative therapy), high (eGFR < 60 ml/min and/or proteinuria > 8g/d for 6 months, or normal eGFR, proteinuria >3.5 g/d, less than %50 reduction in proteinuria after 6 months of conservative therapy and at least one of the following; serum albumin <2.5 g/dl, anti-PLA2R> 50 RU/ml, urinary α-1 microglobulin > 40 μg/min, urinary IgG > 1 μg/min, urinary β -2 microglobulin > 250 mg/d, selectivity index > 2) and very high (life threatining nephrotic syndrome or rapid deterioriation of kidney function) risk patient groups. In low risk group patients non-specific therapy is recommended. Both high and very high risk groups are recommended to treat with immunosuppressive agents in addition to non-specific therapy. Moderate risk patients may be treated by non-specific therapy with or without immunosuppressive therapy depending on patient's status and laboratory changes during follow-up (Rovin et al, 2021).

Initial management should be individualized because of the relatively high spontaneous remission rates. As stated before, both low and moderate risk patients may be followed by only non-specific therapy for 6 months. Patients who have anti-PLA2R antibody levels less than 50 RU/ml are more likely to experience spontanous remission while patients with levels above 150 RU/ml usually require immunosuppressive agents (Hoxha et al,2014; Diaz, Agraz & Soler 2019). Non-specific treatment for 6 months was shown to induce spontaneous remission by the rates of 45% and 34% in patients who had proteinuria >4 g/d and >8 g/d, respectively (Seitz-Polski et al,2018; Pei, Cattran & Greenwood, 1992). Also 20% of spontaneous remission is likely in patients who have anti-PLA2R antibody levels above 275 RU/ml (Dahan et al, 2017). So, we do not have only one parameter to follow in the treatment strategy. Proteinuria degree, serum albumin levels, anti-PLA2R antibody levels and GFR changes during follow-up affects the management decision (Rovin et al, 2021). In anti-PLA2R antibody positive patients, antibody levels may help to reduce side effects of immunosuppressive agents. Because they have long lasting effects, immunosuppressive agents are discontinued after undetectable levels of antibodies are obtained (Tomas, Huber & Hoxha, 2021). Antibody levels should be measured at 3-6 months intervals in patients who have positive antibody levels.

Complete remission is defined as proteinuria below 300 mg/day and serum albumin >3.5 g/dl. Proteinuria between 0.3 to 3.5 g/day with a reduction above 50% from baseline is defined as partial remission (Fervenza et al, 2019).

Treatment:

Conservative therapy should be initiated in all patients with membranous nephropathy, if no contraindication is present. Renin-angiotensin system inhibition in patients with mebranous nephropathy who do not have any contraindication is the mainstay of non-specific therapy. Targeting systolic blood pressure below 120 mmHg, low sodium intake (<2 g/day), low protein diet (0.8-1 g/kg/day), diuretics for edema, treating hyperlipidemia and anticoagulation for appropriate patients are non-specific therapies for patients with membranous nephropathy (Rovin et al, 2021).

With the definition of antibodies, membranous nephropathy became more understood. So, Rituximab was studied on patients with membranous nephropathy. Initial trials showed benefit on remission (Remuzzi et al, 2002; Fervenza et al, 2010). Following studies demonstrated that the response in antibody levels were correlated with with proteinuria degree (Beck et al, 2011). Rituximab was also found to be effective in combination therapy (Fernandez-Juarez et al, 2021; Cortazar, 2017). Further studies were done comparing with other immunosuppressive treatments. In studies comparing Rituximab with Cyclosporine, Rituximab was found to be equally effective with higher long term remission rates and a lower side effect profile (Fervenza et al, 2019; Scolari et al, 2021). Rituximab became a first line treatment option in the management of membranous nephropathy. New guidelines recommend rituximab 1 g iv twice in the first two weeks, then 375 mg/m iv 1-4 times weekly by monitoring the response of proteinuria.

Calcineurin inhibitors are used in the mamagement of membranous nephropathy for many years. Cyclosporine alone is effective in obtaining a remission but have high relaps rates, and the same is true for Tacrolimus (Cattran et al, 2001; Qin et al, 2017; Shang et al, 2018). Cyclosporine plus glucocorticoids promises higher remission rates (Cattran et al, 2001). Tacrolimus plus steroids are similar to cyclophosphamide plus steroids in terms of reaching a remission, but maintaining remission is longer in cyclophosphamide group (Ramachandran et al, 2017). Cyclosporine is recommended 3.5 mg/kg/day with a target through level of 125-225 ng/ml and Tacrolimus is recommended 0.05-0.1 mg/kg/day with a through level of 3-8 ng/ml. Calcineurin inhibitors are given in conjunction with prednisone 10 mg/day. If there is no response at 4 months, calcineurin inhibitors should be withdrawn. If there is response, tapering should be tried after 12 months for a complete of 24 months.

Like calcineurin inhibitors, cytotoxic agents are used in the treatment of membranous nephropathy for a long time (Ponticelli et al, 1984). Cyclophosphamide is preffered over Chlorambucil for its lower side-effect profile (Ponticelli et al, 1998). Either cyclical (modified Ponticelli regimen) or continuous cyclophosphamide therapy can be given. Cyclical therapy is recommended as 1 gr methyprednisolone iv for 3 consecutive days at start of month 1,3,5 and prednisone 0.5 mg/kg/day in the same months is given commutatively with cyclophosphamide 2.5 mg/kg/day in months 2,4 and 6. Contiuous therapy is recommended as 1 gr methyprednisolone iv for 3 consecutive days at start of month 1,3,5 and prednisone 0.5 mg/kg/every other day accompanied by cyclophosphamide 1.5 mg/kg/day in months 1-6.

In patients with anti-PLA2R antibody positive membranous nephropathy, antibody levels should be checked at 3-6 months. If PLA2R antibody is absent at 6 months, treatments with Rituximab and Cyclophosphamide should be stopped while calcineurin inhibitor dose should be tapered. If PLA2R antibody is decreased to low levels; calcineurin group should continue at the same dosage, Cyclophosphamide group can be withdrawn with careful follow-up and Rituximab group should continue with added 2 doses of 1 gr iv two weeks apart. If anti-PLA2R antibody is still present; Rituximab group should continue with 2 grams more Rituximab, Cyclophosphamide group should be changed to Rituximab as starting therapy and calcineurin inhibitors grup should be changed to either Rituximab or Cyclophosphamide treatment (Rovin et al, 2021).

Although the 3 treatment options are recommended as first line, the choice of therapy is decided by the patient's clinical status. In patients with high or very high risk of progression who have declining renal function cytotoxic treatment is preferred. High or very high group of patients with stable renal function Rituximab is preferred, because of prolonged remission compared to calcineurin inhibitors.

Resistant disease is defined as no reduction in proteinuria above 50% from baseline or proteinuria greater than 3.5 g/day. If a patient with membranous nephropathy is resistant to initial treatment, any other initial treatment option should be considered.

Relapsing disease is defined as proteinuria above 3.5 g/day in addition to a >50% increase in proteinuria nadir after a partial or complete remission. Spontaneous remission may also be seen in relaps disease. A six months observation period with conservative therapy is recommended unless there is an indication for immunosuppressive agents, as newly diagnosed disease. Responders to initial cytotoxic therapy should be evaluated carefully for side-effects. Rituximab and calcineurin inhibitors may be a better choice in these patients, particularly in young reproductive individuals. In patients who initially responded to calcineurin inhibitors or Rituximab and have stable renal functions, the same agent may be used. Deterioriation of renal functions should be treated with cytotoxic agents (Rovin et al, 2021).

Treatment of secondary membranous nephropathy is based on treating the underlying disease or withdrawing the offending agent. Anti-PLA2R antibody may be present in patients who have membranous nephropathy with secondary causes. In this case, if there is worsening proteinuria or renal functions -especially in patients with succesfully treated secondary causes- immunosuppressive therapy may be administered (De Vriese, Wetzels & Cattran, 2022). Lupus nephropathy may present with membranous nephropathy. In this case, if there is proliferative findings in pathology, management should be based on the treatment of proliferative disease. If not, only class V lupus nephritis treatment may be enough. Mycophenolic acid analogs, Cyclophosphamide, calcineurin inhibitors and Rituximab should be used along with glucocoriticoids.

Renal transplantation is a good option for end stage kidney disease patients due to membranous nephropathy. Recurrent disease may be observed in approximately 30% of patients and may be higher in anti-PLA2R antibody positive patients (Kattah et al, 2015). Recurrence rates may be over 80% in patients who have high titres of anti-PLA2R antibodies at the time of transplantation (Gupta et al, 2016; Grupper et al, 2015; Kattah et al, 2015; Quintana et al, 2015). However, relaps rates varies between centers. Recurrent disease was found in 8 of 19 (42%) patients in a single center study (Dabade et al, 2008). Recurrent disease is typically observed within 13-15 months after kidney transplantation (Dabade et al, 2008; Sprangers et al, 2010; Ponticelli & Glassock, 2010). Urine protein excretion is recommended to be monitored monthly in the first 6-12 months post-transplantation (Francis & Beck, 2023). Besides, anti-PLA2R antibody levels should be followed at 1-3 months intervals in formerly positive patients. In mild cases only supportive therapy is recommended. In patients with proteinuria above 1 gr/day, Rituximab is recommended as 2 gr in two divided doses 2 weeks apart, along with continuous supportive therapy (Grupper et al, 2016).

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Table1: Secondary causes of membranous nephropathy.

Neoplastic diseases: *Carcinomas (lung, prostate, breast, stomach, colon, renal cell)* *Lymphoproliferative (non-Hodgkin's lymphoma, chronic lymphocytic leukemia)*
Infections: *Hepatitis B virüs* *Hepatitis C virüs* *Human immundeficiency virüs* *Syphilis*
Systemic lupus erythematosus (WHO class V lupus nephritis)
Other immune diseases (rheumatoid arthritis, Hashimato's thyroiditis)
Drugs: *Nonsteroidal antiinflammatory drugs* *Anti-TNF treatment* *Gold* *Penicillamine* *Mercury* *Formaldehyde* *Probenecide*
Sickle cell anemia
Sarcoidosis
Post-transplantation de novo disease due to donor-specific anti-HLA antibodies
Hematopoietic cell transplant/ graft versus host disease

TREATMENT OPTIONS OF TRISMUS AFTER RADIOTHERAPY IN ORAL CANCERS

Niler ÖZDEMİR AKKUŞ
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Introduction

Oral cancers constitute the second most common type of cancer observed in the head and neck region, following skin cancers. Approximately 90% of malignant tumors in this region are squamous cell carcinomas originating from the stratified squamous epithelium (Pauli et al.,2014). The incidence of oral cancer increases with age, with over 95% of patients being above middle age, but there has been an increase in the frequency of oral cancer among young patients as well (Furrer et al., 2006). Squamous cell carcinoma most commonly develops at the lateral borders of the tongue and the floor of the mouth within the oral cavity (Engelmeier & King, 1983). While smoking and alcohol are among the leading etiological factors, it has been reported in recent years that viruses, especially the Human Papillomavirus (HPV), play a role in the development of oral cancer. Despite advancements in early diagnosis and treatment options in recent years, a significant proportion of cases (60-70%) are still diagnosed late, leading to the need for more aggressive interventions and resulting in less favorable functional and cosmetic outcomes (Brizel, 2008).

Worldwide, approximately 600,000 people are diagnosed with head and neck cancer each year, and about two-thirds of these cases are detected at an advanced local stage (Brizel, 2008). While surgical methods are preferred treatment options for certain locations, they can lead to significant functional impairments in areas such as the larynx and hypopharynx. Therefore, in patients with these types of tumors, radiotherapy or chemoradiotherapy is preferred as a radical treatment method. In early-stage head and neck cancer patients with small tumors, minimal spread to surrounding tissues, and no lymph node involvement, radiotherapy alone is generally administered. However, in cases of locally advanced disease with large tumors and lymph node involvement, induction chemotherapy (ICT) followed by or concurrent with chemoradiotherapy (CRT) has been reported to increase overall survival, disease-free survival, and reduce the risk of death (Pignon & Baujat & Bourhis, 2005), Pignon et al., 2000).

The effects of radiotherapy in head and neck cancers

Due to the radiobiological characteristics of tumors in head and neck cancer patients, higher doses of radiation therapy (RT) are necessary. Additionally, the head and neck region contains numerous normal tissues and organs with low tolerance doses. Therefore, side effects related to RT are observed much more frequently and intensely compared to other regions. Furthermore, since CRT (chemoradiotherapy) is the standard treatment for most head and neck cancer cases, acute side effects associated with RT are significantly increased (Fulton & Middleton, 2002). Treatment-related oral complications can occur acutely during or immediately after treatment, and in some cases, cancer therapy can lead to long-lasting oral issues. The frequency and severity of oral complications vary depending on the type and dosage of cancer treatment, as well as individual differences. The most significant oral complications associated with chemotherapy are mucositis, which mainly develops during and immediately

after treatment, and oral infections caused by various pathogens. In contrast, radiation therapy directly affects the epithelium, salivary glands, bone, and muscles, leading to both acute and chronic complications (Engelmeier & King, 1983), (Sonis & Woods, 1990).

Mucositis

Mucositis is a significant side effect characterized by ulceration and inflammation of the oral mucosa, and it can serve as a source of life-threatening infections associated with cancer treatments. This condition can lead to a decrease in the patient's quality of life, an increase in palliative treatment costs, both oral and serious systemic infections, and a risk to the continuation of treatment (Engelmeier & King, 1983), (Hancock , Epstein & Sadler, 2003).

Oral infections

The frequency of oral infections is increased in cancer patients due to immunosuppression. The most common oral infection seen is candidiasis. Poorly controlled oral candidiasis can increase the risk of aspiration and lead to conditions such as Candida esophagitis (Engelmeier & King, 1983), (Soysa, Samaranayake & Ellepola, 2004).

Xerostomia

Another complication of radiotherapy is xerostomia (Barasch & Peterson, 2003). It becomes more pronounced when chemotherapy and radiotherapy are administered together (Epstein et al, 2004). It particularly affects the acinar cells in serous salivary glands such as the parotid gland due to the effects of radiotherapy. The prevalence, duration, and reversibility of xerostomia depend on the radiation dose and the radiation field. When radiotherapy exceeds a total of 60 Gray in cases of head and neck tumors, there is a loss of salivary gland function of approximately 80%, which is generally irreversible. If xerostomia persists for more than twelve months, it usually does not resolve spontaneously (Soysa, Samaranayake & Ellepola, 2004), (Harrison et al., 2003).

Osteoradionecrosis

Osteoradionecrosis is the rapid and irreversible loss of vitality in bone that has been exposed to radiation (Hancock , Epstein & Sadler, 2003). It is more commonly observed in the mandible due to its poor vascularity and high bone density (Rubenstein et al., 2004). In irradiated bone, vascular channels narrow, blood flow decreases, and there is a decrease in the number of osteocytes, resulting in a reduced potential for bone healing. It is not a true osteomyelitis but rather occurs due to impaired wound healing resulting from decreased vascularity associated with radiation therapy (Harrison et al., 2003). Most cases generally occur within a few years after radiotherapy, but the risk of developing osteonecrosis exists at any time following radiotherapy (Hancock , Epstein & Sadler, 2003).

Trismus

Trismus is defined as tonic contraction of the masticatory muscles. In the past, it was mainly used to describe the effects caused by tetanus and was known as "lockjaw." However, in recent years, it is used to explain restrictions in mouth opening due to any cause. Trismus is a symptom that dramatically affects the quality of life. Inability to open the mouth adequately can lead to impaired articulation, reduced oral cavity volume affecting vocal quality, making communication difficult. In cases of severe trismus, oral hygiene, chewing, and swallowing functions are negatively impacted, increasing the risk of aspiration.

Restrictions in jaw movements can result from muscle, joint damage, rapid proliferation of connective tissue, or a combination of these factors. The causes of trismus can be grouped

into intra-articular and extra-articular categories. Additionally, central nervous system disorders such as tetanus, lesions affecting the trigeminal nerve, or drug toxicity can also lead to this condition. Damage to each of the masticatory muscles (temporal, masseter, medial and lateral pterygoids) can result in limitations in mouth opening. Pain reflex is stimulated with muscle damage, leading to contraction and restriction of movement. On the other hand, mandibular hypomobility causes degenerative changes in the muscles and joint within a few days. The muscles undergo atrophy, while the synovial fluid in the joint becomes denser and the cartilage becomes thinner

Trismus can be a symptom of oncological diseases, and sometimes it is a delayed side effect that occurs after radiation therapy (RT) to the head and neck region. Trismus following radiation therapy develops slowly, and it may not be noticed for months. Additionally, patients may consider this condition as normal or overlook it due to the already challenging nature of eating solid foods caused by dry mouth (Ichimura & Tanaka, 1993), (Goldstein et al., 1999).

For effective and efficient treatment of radiation-induced fibrosis, it is crucial for clinicians to understand its pathogenesis. Radiation-induced fibrosis arises from a localized inflammatory response, leading to a series of events such as excessive collagen accumulation, impaired local circulation, and formation of scar tissue (Straub et.al., 2015). This condition is associated with high levels of upregulation of transforming growth factor-beta (TGF-beta) (Lyons, Crichton & Pezier, 2013), (Peng et al., 2016), Baldoman & Vandenbrink, 2018).

Radiation-induced fibrosis in the head and neck region can lead to neuromuscular complications due to ectopic nerve activity and nerve atrophy. Symptoms such as musculoskeletal pain, spasms, and muscle weakness may arise. In head and neck cancer, examples of conditions associated with radiation-induced fibrosis include trismus (restricted mouth opening), neck extensor muscle weakness, and cervical dystonia. Magnetic resonance imaging of patients with trismus can reveal fibrosis symptoms affecting not only the masticatory muscles but also surrounding tissues. This can manifest as thickening of the temporomandibular joint (TMJ) capsule and signs of osteoradionecrosis affecting the mandible (Pauli et al., 2014).

Trismus typically occurs 4-12 months after radiation therapy, progresses rapidly within the first 9 months, and can persist for years. It can occur as a result of rapid collagen formation and the involvement of the medial pterygoid muscle in the treatment field or the development of muscular fibrosis in the masticatory muscles. The severity of trismus can vary depending on the radiation field (salivary glands, mandible, maxillary tumors, nasopharynx, base of the tongue), dosage, and the patient's tolerance (Vissink et.al., 2003). Goldstein et al. (1999) suggested that the most significant factor determining the development of trismus may be the involvement of the medial pterygoid muscle in the treatment field. Trismus has been reported to develop around 3-6 months after treatment when the masticatory muscles are involved, leading to muscular fibrosis and sclerosis (Dijkstra, Huisman & Roodenburg, 2006).

Trismus may develop slowly, and patients may not notice it until their mouth opening is 20 mm or less. The degree of trismus can vary, with mouth opening ranging from 20-40 mm. If the mouth opening is less than 30 mm, it is considered mild trismus; between 15-30 mm is classified as moderate trismus, and less than 15 mm is classified as severe trismus (Khare et al., 2012).

Trismus treatment

Although several methods have been described for the treatment of trismus, there is a lack of large-scale prospective randomized studies evaluating the effectiveness of different

approaches. There is no clear consensus on how exercise programs should be designed, and the course of treatment may vary depending on the individual patient (Pauli et al., 2014).

Many medical devices have been designed to assist in the rehabilitation of trismus. While some of these trismus devices have appropriate regulatory approvals, many are temporary devices adapted from their original uses (e.g., stacked wooden tongue depressors) or experimental devices that have not undergone suitability assessments. These devices are often combined with range of motion (ROM) exercise programs and used either as preventive programs during radiation therapy or as intensive post-treatment or maintenance programs. Combining trismus devices with exercise programs seems intuitive, but determining the independent effects of the device can be challenging when exercise programs vary. Additionally, when the course of trismus (stable, worsening, or improving) is unknown, it is impossible to determine if the intervention (device-related) is associated with the improvement (Charters et al., 2022).

According to the current literature, rehabilitative approaches aimed at preventing trismus may involve the application of passive or active stretching to the mandible, which can include the use of jaw mobilization devices such as TheraBite (Atos Medical, Horby, Sweden) or Dynasplint (Dynasplint Systems, Inc., Maryland, USA), as well as devices like stacked tongue depressors. In recent years, advances in treatment techniques such as intensity-modulated radiation therapy (IMRT) have significantly reduced the prevalence of trismus and improved functional outcomes. However, given the disabling nature of trismus, the need for evidence-based approaches to preventive and therapeutic rehabilitation persists. Preventive and therapeutic rehabilitation for trismus is considered standard care, but there is currently no consensus on a rehabilitation protocol (Chee et al., 2021).

Jaw exercise

Most treatment methods are based on stretching the muscles of mastication and the TMJ. The stretching can be performed either using a jaw exercise device, which assist mouth opening or unasissisted using manual stretching with the fingers to force mouth opening (Pauli et al., 2014).

Exercise therapy is the centerpiece of radiotherapy-induced trismus management. It must begin early after radiation to be effective (Rapidis et al., 2015). It is important to recognize the etiology for reduced MID. Mouth-opening limitation could be intra-articular and/or extra-articular in origin; therefore, a detailed examination is required. The physical therapist commonly performs an assessment of posture, neck mobility, and the TMJ including intra-oral joint testing and palpation of muscles of mastication. In most cases of radiotherapy-induced trismus, muscles of mastication become stiff and rigid, limiting muscle extensibility (Baldoman & Vandenbrink, 2018).

Exercises, when combined with jaw-mobilizing devices, have proven to be the most effective strategy in increasing MID (Scherpenhuizen et al., 2015). Physical therapist supervision of jaw-mobilizing device use is critical as there are factors that warrant patient understanding for the treatment to succeed, especially in first 4–6 weeks. For example, when patients experience pain in the process without a Professional guiding them and helping control pain, early termination of treatment could result. The first 4 weeks is also when patients can regain the largest increase in mouth opening with jaw-mobilizing device. Manual therapies such as masticatory muscle stretching and massage, temporomandibular/cervical joint mobilization, and myofascial release to neck musculature also augment the effectiveness of treatment (Calixtre et al., 2015).

Two of the most commonly utilized and studied jaw-mobilizing devices are TheraBite (Atos Medical, Horby, Sweden) and Dynasplint (Dynasplint Systems, Inc., Maryland, USA). With TheraBite, patients manually squeeze the handle to apply torque, while with Dynasplint, patients incrementally increase torque and jaw opening by turning a handle. Such differences become important when chemotherapy-induced neuropathy impairs grip strength for TheraBite usage (Addington & Freimer, 2016). In addition, painful rebound muscle spasms, which cause setbacks, can potentially occur if the torque is exceeded. Once maximum MID has been reached, patients are advised to maintain daily stretching, as MID may regress quickly without continued usage.

A low torque-sustained stretch was superior to a high-torque short duration stretch in lengthening muscle contracture in an animal study (Usuba et al., 2007). In a prospective intervention study using TheraBite in a structured 10-week exercise program (30 s hold of passive stretch five times daily), the mean increase in MID was 7.2 mm after 3 months, with concurrent improvement in quality of life (Pauli et al., 2014). In a preliminary report using Dynasplint, an 11 mm improvement in MID was demonstrated after using the device 30 min three times daily for 3 months in combination with physical therapy, pain medications, and botulinum toxin injections (Stubblefield, Manfield & Riedel, 2010). Despite their benefits, jaw mobilization devices are expensive and not often covered by insurance: TheraBite is available for purchase for $500 while Dynasplint is usually for rent at $300 monthly. Of note, when initial mouth opening is less than 7 mm, exercises often starts with stacked tongue depressors since most jaw-opening devices would require a minimum MID to be utilized (Buchbinder et al., 1993).

Other mechanical alternatives

Numerous alternative treatments for trismus have been proposed. Examplaes are rubber plugs inserted between the jaws as screws or tongue depressors stacked in a pile to gradually force mouth opening. Exercises that aim to increase the range of motion of the lower jaw can be recommended in addition to initial exercises. These exercises involve opening and closing the mouth and moving the mouth from side to side for five minutes every three to four hours. To enhance exercise compliance and treatment effectiveness, therapeutic adjunctive devices such as stacked wooden tongue depressors can be used during the exercises (Pauli et al., 2014).

Pharmacological treatment

Pharmacological treatment alternatives fort he treatment of trismus have been described. Botulinum toxin, injected transcutaneous into the masseter muscles reduces pain in patients with trismus but does not improve mouth opening (Pauli et al., 2014).

Adjunctive/Alternative Therapies

There are adjunctive therapies that have shown some benefits. They are not yet widely accepted due to lack of robust empirical data to support their use. In a pilot study specifically addressing RIT, pentoxifylline, given at a dose of 400 mg two to three times daily for 8 weeks, resulted in a mean increase of 4 mm in MID (Chua et al., 2001). At another study using case-control, neuromuscular electrical stimulation using surface electrodes twice weekly for an hour after each radiation therapy in the clinic with traditional swallow therapy done 2 weeks before and ended 2 weeks after the course of radiation therapy helped prophylactically reduce fibrosis in muscles (Peng et al., 2016).

Multiple approaches have been recommended for the management of trismus including therapeutic exercises, electrotherapeutic modalities, computer-based equipment, and in some cases surgical interventions (Buchbinder et al., 1993). Other modalities such as stretching

exercises that incorporate moist heat, low intensity ultrasound (LIUS) and transcutaneous electrical nerve stimulation (TENS) are preferred due to their ease of application and efficiency (Elgohary et al., 2018). LIUS is a modality used for the treatment of many skeletal muscle dysfunctions. Its mechanical energy, is transferred in the manner of acoustic compression waves to evoke thermal and mechanical physiological changes in the targeted tissue. This particular feature makes LIUS a common modality used for treatment. It was assumed that the mechanical strains of ultrasound provoke biochemical changes which accelerate the tissue repair. The thermal physiological changes of LIUS include the increment of local tissue temperature, plenty of blood flow and improvement of the flexibility and extensibility of tissue with diminished fluid viscosity making LIUS applicable in the management of trismus condition and for diminishing TMJ pain following HNC (Hashish, Harvey & Harris, 1986).

Neuromuscular stabilization is an example of a manual therapy technique used for the treatment of TMJ dysfunction (McNeely, Armijo & Magee, 2006). The mastication muscles is used to implement a compressive power to the condylar disk through promoting the condylar-disk-eminence integrity and eventually recovering the muscle function. These procedures can additionally be employed as proprioceptive training to develop functional movements and concurrently diminishing pain (Nicolakis et al., 2001).

Low level laser therapy (LLLT) reduces the inflammatory conditions without adverse consequences by lessening pain and swelling and supporting the repair of the tissue (Ferrante et al., 2013). The force of LLLT in treating pain originating from soft-tissue trauma can be attributed to the indirect reduction of edema, bleeding, neutrophil activity, provocative cytokines and enzymatic action. LLLT reduces swelling and subsequent pain resulting in, enhanced tissue repair since lymphatic vessels regeneration is accelerated and the vascular permeability is minimized (Alan et al., 2016).

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Possible Diagnostic Markers Related To Gastroinstestinal Dysfunction In Critically Ill Patients

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Introduction:

Critical illness is a condition in which life-threatening complications develop, pharmacological and mechanical treatment is required, multiple-organ failure is seen, and long-term intensive care treatment is required (Geen et al., 2021; Reintam et al., 2008; Schweickert et al., 2004). Gastrointestinal complications, which are common in critically ill patients, can lead to negative outcomes. Recently, it has been reported that the incidence of gastrointestinal dysfunction (GID) or gastrointestinal failure (GIF) in patients in care units is approximately 40% and the mortality is 33% (Sun et al., 2020). Enterocyte damage has been found in approximately 50% of critically ill patients in intensive care units (ICU) with widespread GID (Li et al., 2017). Critically ill patients with GID have a poor prognosis and a high mortality rate (Asrani et al., 2020; Li et al., 2017; Piton et al., 2011).

To identify critically ill patients treated in the ICU and to predict risk stratification, the indicative scores such as the Acute Physiology and Chronic Health Assessment (APACHE) score, the Simplified Acute Physiology Score (SAPS), and the Trauma and Injury Severity Score (TRISS) score are preferred (Hwang et al., 2012; Nik et al., 2018; Wong et al., 1996). In addition, Sequential Organ Failure Assessment (SOFA) score is used to define sepsis criteria and sequential multi-organ failure in ICUs in determining the risk of mortality (Lambden et al., 2019; Song et al., 2018). It is known that disease scoring is important in terms of determining the mortality rate in the ICU, the development of multiple organ failure, and the evaluation of treatment efficacy, and that these scoring results support each other (Czajka et al., 2020; Hwang et al., 2012; Reintam et al., 2008).

In critically ill patients, classification is made according to SOFA and APACHE II criteria to follow the development of organ failure and the prognosis of the patient. However, there are no definitive criteria, laboratory findings, or imaging techniques to define GID in these scorings (Reintam et al., 2008; Reintam Blaser et al., 2020). Various study groups have developed a GID score by adding SOFA and APACHE II scores and various criteria to determine GID in

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critically ill patients. According to the results of these studies, it was determined that the survival rate was low in critically ill patients with GID (Reintam et al., 2008; Reintam Blaser et al., 2021). In addition, many studies have emphasized that GID plays an important role in organ failure in critically ill patients (Clark & Coopersmith, 2007; Mayr et al., 2006; Perez-Calatayud et al., 2018). Therefore, the identification of GID in critically ill patients will also be decisive in the epidemiology of the disease, risk factors, and development of the treatment options, moreover it will support currently being used scores.

GID, which is common in critically ill patients, has at least one gastrointestinal symptom such as intolerance, ileus, diarrhea, digestive bleeding, or intestinal ischemia during their stay in the ICU (Asrani et al., 2020). These symptoms may occur mostly as a result of deterioration of mucosal integrity, absorption problems, changes in microbiota, increased intra-abdominal pressure, or various diseases (Reintam Blaser et al., 2020; Typpo et al., 2022).

The intestinal barrier is a protective component of the intestine and protects us against toxins or bacterial invasion of microorganisms. Intestinal permeability is a measurable property of the intestinal barrier (Li et al., 2017). The intestinal epithelium is a unicellular layer that forms a barrier against the external environment. It provides an effective defense against intraluminal toxins, antigens, and enteric flora while acting as a selectively permeable barrier allowing the absorption of nutrients, electrolytes, and water (Groschwitz & Hogan, 2009). Epithelial cells form three adhesive complexes: tight junctions, adherens junctions, and desmosomes (Bayarri et al., 2021). Disruption of the intercellular connection causes the bacteria and their metabolites to pass into the circulation through epithelial cells. Therefore, the adhesion of intestinal epithelial cells to each other and the protection of these structures are very important for intestinal health (Rombeau & Takala, 1997).

The gastrointestinal tract found in the human body has extensive colonization in the human intestinal flora for more than 1500 species. In recent metagenomic studies, it has been shown that intestinal flora plays an important role in human health such as gastrointestinal diseases, such as diabetes, colon cancer, extragastrointestinal diseases, inflammatory bowel disease, irritable bowel symptoms, coronary heart disease, and obesity (Li et al., 2020). Gastrointestinal (GI) complaints account for 11% of all hospitalizations. It also shows a positive relationship between patient physiological processes and microbiome variability (Holmes & Blanke, 2019).

GID causes worse clinical outcomes in critically ill patients (Reintam Blaser et al., 2013). Dysfunction of the gastrointestinal tract is a common occurrence in traumatic brain injury (TBI) (Katzenberger et al., 2015). Currently, there are no known reliable tools for monitoring gastrointestinal function in critically ill patients. Biomarkers are therefore of great interest in this field. Because the lack of monitoring tools is one of the biggest obstacles to interventional studies (Hwang et al., 2012).

In some studies, intestinal fatty acid-binding protein (I-FABP), D-Lactate, lipopolysaccharide (LPS), and citrulline were recommended as biomarkers for intestinal barrier function in critically ill patients with intestinal barrier dysfunction (Blaser et al., 2019; Donmez-Altuntas et al., 2023; Ewaschuk et al., 2005; Fragkos & Forbes, 2018; Ghosh et al., 2020; Li et al., 2017; Monroe et al., 2019; Moonen et al., 2019; Peoc'H et al., 2018; Piton et al., 2011; Pohanka, 2020; Shi et al., 2015; Voth et al., 2017). It has been shown that there is a significant difference between the APACHE II score, I-FABP, D-lactate, and LPS levels in the evaluation of the relationship of other clinical variables with the degree of acute gastrointestinal injury and the relationship of these clinical variables with mortality (Li et al., 2017). Blaser et al. (2021) developed a scoring system that defines GID in critically ill patients and includes bowel barrier functions such as I-FABP, LPS, and D-Lactate, but they could not make a definite

recommendation for the use of these markers in the diagnosis of GID (Reintam Blaser et al., 2021).

In this respect, intestinal barrier function can be measured by assaying biomarkers such as I-FABP, D-Lactate, LPS, and citrulline (Figure 1). In this review, we summarized the evolving importance of these biomarkers in understanding of the molecular composition and regulation of intestinal barrier function in critically ill patients.

LPS

LPS is an important component of the cell wall structure of gram-negative bacteria, is abundant throughout the GI tract, and causes acute inflammation and septic shock. LPS may also triggers chronic inflammation (Ghosh et al., 2020). LPS found in food and the source of LPS is an increase in endogenous production, which is usually maintained by the gut microbiota. The inflammatory effect of LPS appears first in the gut so that both gut microbiota and gut-associated lymphoid tissue are affected by LPS and shift towards an inflammatory pattern (Candelli et al., 2021). The main source of LPS in healthy individuals is the microbiota. The increase in LPS level only occurs when inflammation begins. But this information may be partial because different bacteria have been observed to produce different types of LPS, some of which are more likely to detect an inflammatory response (Candelli et al., 2021). For example, the LPS of Bacteroides is relatively harmless and LPS produced by E. coli is the highly toxic (Vatanen et al., 2016). Recent developments have revealed the mechanisms by which the intestinal mucosal barrier is regulated in response to physiological and immunological stimuli. The GI tract is thought to be made permeable to LPS through changes in tight junctions (Turner, 2009). Increased serum LPS levels may reflect increased intestinal permeability and impaired GI barrier function in critically ill patients (Li et al., 2017).

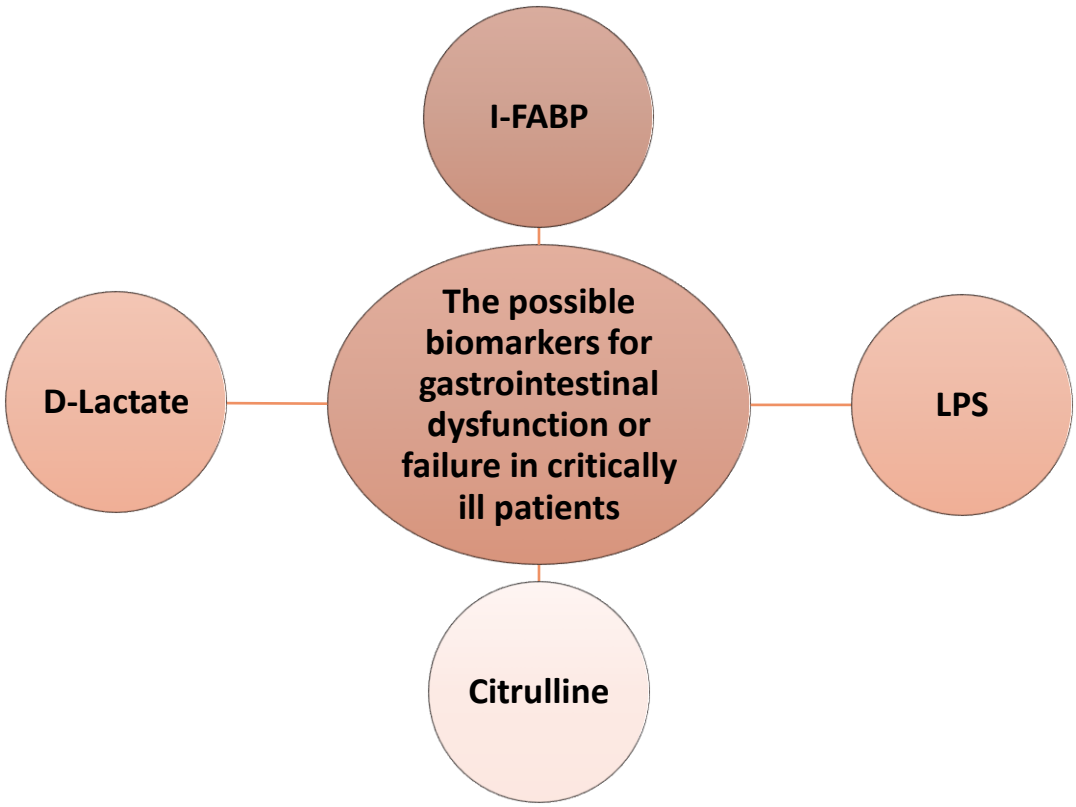

Figure 1. The possible biomarkers in related to the gastrointestinal dysfunction or failure in critically ill patients

I-FABP

I-FABP is a small (15 kDa) cytosolic protein found only in mature epithelial cells of the small and large intestine and is released by enterocytes in the intestine (Blaser et al., 2019; Shi et al., 2015). They play a role in the transport of fatty acids from the apical membrane to the endoplasmic reticulum (Grootjans et al., 2010). In case of tissue or organ damage, they are released in high amounts into the extracellular space (Blaser et al., 2019; Shi et al., 2015). I-FABP has been studied as a marker in many intestinal injuries, such as intestinal ischemia, intestinal injuries, and necrotising enterocolitis, and it has been shown that serum or plasma levels increase in such conditions (Blaser et al., 2019; Heida et al., 2015; Shi et al., 2015; Voth et al., 2017). The high plasma I-FABP concentrations were associated with bacterial translocation causing intestinal ischemia, severe acute pancreatitis, celiac disease, infected necrosis, and organ failure. Thus, I-FABP levels are correlated with bacterial translocation and small intestinal permeability (Blaser et al., 2019; Piton et al., 2011; Shi et al., 2015).

I-FABP levels, which is associated with intestinal ischemic injury, may be a biomarker for the gastrointestinal tract function. Moreover, plasma concentration of this protein are also susceptible to liver or kidney dysfunction in critically ill patients (Blaser et al., 2019; Li et al., 2017; Shi et al., 2015).

D-Lactate

D-lactate is produced exogenously by the intestinal flora bacteria, such as lactobacilli and bifidobacteria, and by contaminated foods, or endogenously by the metabolism of small amounts of methylglyoxal (Ewaschuk et al., 2005; Monroe et al., 2019). Although D-lactate is produced in very small amounts in mammalian cells, the D-lactate level may increase due to microbial production. D-lactate can be used as a diagnostic marker for appendicitis, gastrointestinal diseases, intestinal ischemia in abdominal compartment syndrome and in acute abdomen patients, and GID in critically ill patients (Teng et al., 2021).

In fact, in mammals, lactide exists in the form of L-lactate, but in the case of bacterial fermentation, it is converted to D-lactate. Likewise, D-lactate, which is seen in the GI tract, is a bacterial fermentation product (Ewaschuk et al., 2005). It has been shown that serum D-lactate levels increase because of impaired intestinal permeability (Ewaschuk et al., 2005; Monroe et al., 2019; Seheult et al., 2017).

Citrulline

Citrulline is a non-protein amino acid, which is an end product of glutamine metabolism and a metabolite of arginine. In humans, most of the plasma citrulline content is produced in enterocytes of the small bowel. Therefore, citrulline production in the whole body is almost exclusively provided from the small intestine epithelium (Papadia et al., 2018). Thus, plasma citrulline levels are used as a marker for enterocyte mass and intestinal malabsorption (Ewaschuk et al., 2005; Peoc'H et al., 2018).

Citrulline in biological matrices is often measured as part of an amino acid profile. But it remains a challenge due to time-efficient and extensive quantification, poor chromophore and fluorophore response, zwitterion functionality, and diversity, greatly exceeding the typically 21 proteinogenic amino acids from complex biological matrices (Blaser et al., 2019).

Citrulline is a non-essential amino acid involved in the urea cycle as a mediator of both arginine and glutamine. The production of citrulline is almost entirely produced from glutamine in the mitochondria of mature enterocytes of the small intestine. It is excreted only by being converted to arginine in the kidney (Blaser et al., 2019; Candelli et al., 2021; Li et al., 2017). The circulating citrulline levels in humans plays a role as a functional intestine biomarker. Citrulline are related to a decrease in enterocyte mass and loss of citrulline level, which is

considered a biomarker for GIF, in critically ill patients. In addition, the plasma citrulline level in clinical practice serves as an indicator of small bowel function (Teng et al., 2021).

Generally, a low citrulline level (<20 mmol/L) was suggested as a GID marker in critically ill patients (Atasever et al., 2018). This situation is mostly associated with malnutrition (Blaser et al., 2019). In some clinical studies, low citrulline levels in plasma have been associated with epithelial damage, bacteraemia, and GID (Herbers et al., 2008; Pan et al., 2010; Van Vliet et al., 2009).

Conclusions

GID is common in critically ill patients and usually associated with a poor prognosis. Although a GID score developed by adding SOFA and APACHE II scores and various criteria in critically ill patients, there are no definitive criteria, laboratory findings, and imaging techniques to determine GID. Recently, the focus has been on identifying biological markers that define GID in critically ill patients. The biomarkers such as plasma levels of I-FABP, D-Lactate, LPS and citrulline may be recommended as possible markers of intestinal barrier function and may help in the early diagnosis and treatment of GID or GIF in the follow-up of critically ill patients.

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Radıologıcal Fındıngs In Pulmonary Embolısm

Zeliha COŞGUN

Introduction

Pulmonary thromboembolism, also known as pulmonary embolism (PE), is characterized by the obstruction of the pulmonary arterial system due to the presence of emboli. The primary cause of this condition is the formation of blood clots, leading to thrombotic occlusion. The clinical presentation of PE encompasses various aspects that aid in its diagnosis. Patients may provide a medical history indicating recent immobilization or surgery, active malignancy, hormone usage, or a prior episode of thromboembolism. During the physical examination, certain suggestive features may be observed. These include clinical signs of deep venous thrombosis, characterized by asymmetric pitting lower extremity edema, the presence of prominent superficial collateral vessels, and tenderness to palpation along the deep venous system. Additionally, patients may exhibit tachycardia, dyspnea, pleuritic chest pain, or even hemoptysis (Moore & et al., 2017)

Pulmonary thromboembolism is a serious medical condition, and understanding its associated risk factors is crucial for risk assessment, prevention, and management. Several risk factors have been identified in the development of PE. Primary hypercoagulable states, such as protein C deficiency, protein S deficiency, antithrombin III deficiency, lupus anticoagulant, and factor V Leiden mutation, significantly increase the risk of PE. Recent surgical procedures, particularly those involving the lower extremities or the abdomen, have been found to elevate the risk of PE. Prolonged bed rest or immobility is also a significant risk factor due to the increased likelihood of venous stasis and subsequent blood clot formation. Malignancies, including multiple myeloma, have been associated with an increased risk of PE. Patients with HIV infection face a 2 to 10 times higher risk of PE compared to non-HIV matched controls (Moore & et al., 2017). Moreover, COVID-19 infection has emerged as an additional risk factor for PE (Danzi & et al., 2020). Certain medications, such as oral contraceptives, thalidomide, and lenalidomide, have been identified as risk factors for PE due to their potential to promote blood clot formation. Pregnancy poses a higher risk of PE due to the physiological changes that enhance blood coagulation. Individuals with a known or previous history of deep venous thrombosis are also at an increased risk of developing PE. Lastly, the presence of certain venous aneurysms, such as popliteal venous aneurysm, is associated with an elevated risk of blood clot formation and subsequent PE. Recognizing and understanding these risk factors is paramount for effective risk assessment, implementing preventive measures, and ensuring appropriate management strategies for individuals at risk of developing PE (Han & et al., 2003).

In the evaluation of PE, certain markers are utilized to aid in the diagnostic process. One commonly used marker is D-dimer, which is measured using the ELISA method. In patients with a low or moderate probability clinical assessment, a normal D-dimer level demonstrates an almost 100% negative predictive value. This means that if the D-dimer level is within the normal range, it effectively excludes the presence of PE, and no further testing is necessary. However, it is important to note that a raised D-dimer level is not specific to PE and can be

elevated in various other conditions. Therefore, a raised D-dimer indicates the need for further testing if PE is suspected, as it does not provide a definitive diagnosis on its own (Corwin & et al., 2009). On the other hand, in patients with a high probability clinical assessment, the D-dimer test is not as helpful. This is because even if the D-dimer result is negative, it does not exclude the possibility of PE in more than 15% of cases. In such situations, patients are typically treated with anticoagulants while awaiting the outcome of additional diagnostic tests. The use of markers, such as D-dimer, aids in the diagnostic process of PE, providing valuable information for risk stratification and determining the need for further testing or treatment. Understanding the limitations and interpretation of these markers is crucial for accurate diagnosis and appropriate management of patients suspected of having PE (Corwin & et al., 2009).

Hemodynamic classification is crucial in assessing the severity and clinical presentation of PE. PE can be classified into different categories based on its hemodynamic impact. Massive PE refers to a high-risk situation where there is hemodynamic instability, often resulting in cardiogenic shock or sudden cardiac arrest. Submassive PE, on the other hand, is characterized by hemodynamic stability but evidence of right ventricular dysfunction or myocardial injury. To further assess the risk and prognosis of PE, a risk stratification system is used. This system categorizes PE into low-risk, intermediate-risk (submassive), and high-risk (massive) based on various clinical parameters and imaging findings. Temporal pattern is another important aspect in understanding PE (Ocak & Fuhrman, 2008) . It can be classified into acute, subacute, or chronic based on the duration and progression of symptoms. Acute PE refers to a sudden onset of symptoms, often within a few hours or days. Subacute PE describes symptoms that have been present for days to weeks (Stein & et al., 2007). Chronic PE refers to long-standing or recurrent PE. In terms of the involvement of pulmonary vessels, PE can be classified anatomically. The main vessel affected in PE is the pulmonary artery. A saddle embolus refers to a clot that spans the bifurcation of the main pulmonary artery. Lobar, segmental, and subsegmental emboli describe the involvement of progressively smaller branches of the pulmonary artery (Castañer & et al., 2009). Understanding these hemodynamic, risk, temporal, and anatomical classifications is essential in the diagnosis, management, and prognosis of patients with PE. It helps guide appropriate treatment strategies and contributes to improved patient outcomes.

Chest radiodraphy findings

Chest radiography lacks both sensitivity and specificity in diagnosing PE. Its primary purpose is to evaluate alternative diagnostic possibilities such as pneumonia and pneumothorax, rather than serving as a direct tool for PE diagnosis.

Several chest radiographic signs have been described in relation to PE

Fleischner sign: This sign indicates an enlarged pulmonary artery and is observed in approximately 20% of cases.

Hampton hump: It manifests as a peripheral wedge-shaped opacity in the airspace and suggests lung infarction. This sign is also present in about 20% of cases.

Westermark sign: This sign reveals regional oligemia and holds the highest positive predictive value at around 10%.

Pleural effusion: Pleural effusions can be observed in approximately 35% of PE cases.

Knuckle sign: This sign is documented in the literature as Knuckle 11, although further details are not specified.

Palla sign : It denotes an enlarged right descending pulmonary artery.

Chang sign : This sign signifies a dilated right descending pulmonary artery with sudden changes (Worsley & et al., 1993).

CT Findings

CT (computed tomography) plays a crucial role in the evaluation of acute pulmonary emboli. CT pulmonary angiography (CTPA) is particularly effective in visualizing filling defects within the pulmonary vasculature caused by acute pulmonary emboli. When the pulmonary artery is viewed in the axial plane, the central filling defect resulting from the thrombus is surrounded by a thin rim of contrast, which has been referred to as the Polo Mint sign (figure 1). Emboli can be occlusive or non-occlusive, with the latter exhibiting a thin stream of contrast adjacent to the embolus. Acute emboli typically form an acute angle with the vessel, distinguishing them from chronic emboli. The affected vessel may also enlarge in size. In rare cases, acute pulmonary thromboemboli can be detected on non-contrast chest CT as intraluminal hyperdensities (Wittram & et al., 2004).

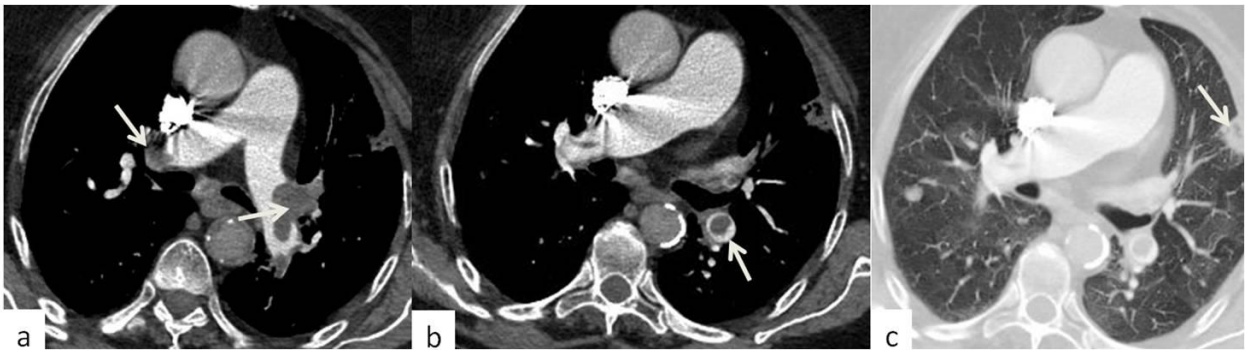

Figure1: In a 90-year-old woman presenting with shortness of breath, filling defects consistent with emboli are observed in both main pulmonary arteries distally (a, arrow). On axial imaging, the Polo Mint sign indicative of acute emboli is seen (b, arrow). Associated parenchymal infarction is demonstrated in the parenchymal window (c, arrow). A pulmonary nodule is also visualized in the accompanying right lung.

In contrast to acute PE, chronic thromboemboli are often characterized by complete occlusions or non-occlusive filling defects located in the periphery of the affected vessel, forming obtuse angles with the vessel wall. It is not uncommon for the thrombus in chronic cases to exhibit calcification.

Chronic PE display specific features, including the presence of webs or bands and intimal irregularities. There may be abrupt narrowing or complete obstruction of the pulmonary arteries(figure 2). Another notable characteristic is the occurrence of "pouching defects," which refer to chronic thromboembolism organized in a concave shape that points toward the vessel lumen Indirect signs associated with chronic PE encompass mosaic perfusion, vascular calcification, and bronchial or systemic manifestations(Castañer & et al., 2009); (Wittram & et al., 2006).

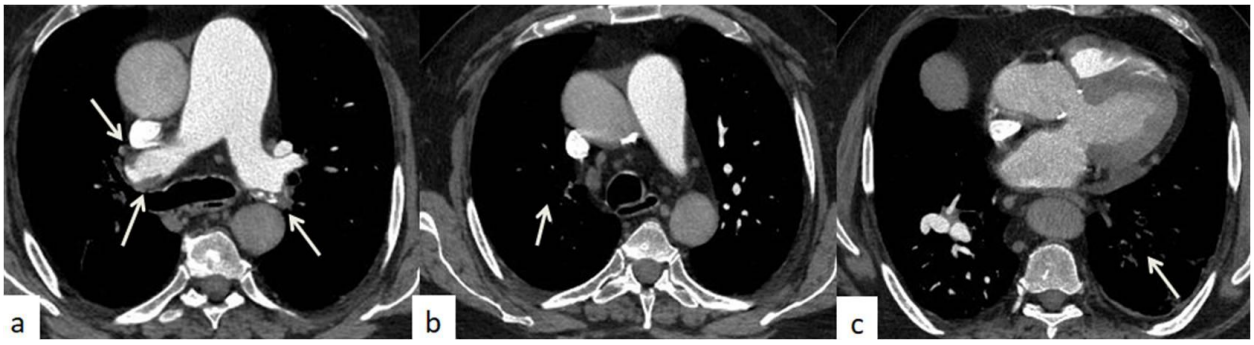

Figure2: In a 77-year-old man presenting with shortness of breath, "In the right main pulmonary artery, there is a chronic thrombus (a) allowing contrast passage, while in the left main pulmonary artery, there is calcification within the thrombus. Additionally, there is reduced calibration in the right main pulmonary artery upper lobe-segmental branches (b) and in the left main pulmonary artery lower lobe-segmental branches.

Complications of Acute Pulmonary Emboli

In cases of large obstructing saddle emboli, pulseless electrical activity (PEA) may occur. Right ventricular dysfunction is a common complication associated with both acute and chronic emboli. CT features indicative of right ventricular dysfunction include abnormal positioning of the interventricular septum, contrast reflux in the inferior vena cava, and a right ventricular diameter (RVD) to left ventricular diameter (LVD) ratio greater than 1 on reconstructed four-chamber views. However, a RVD:LVD ratio greater than 1 on standard axial views is not considered a reliable predictor of right ventricular dysfunction (Ocak & Fuhrman, 2008).

When right ventricular dysfunction is demonstrated on imaging (CT or echocardiography) without significant hemodynamic compromise, it is referred to as submassive PE. Subacute-to-chronic PE can lead to complications such as pulmonary infarction, pulmonary hypertension, and ultimately, the development of cor pulmonale (Kang & et al., 2011). Approximately 80% of pulmonary emboli tend to resolve within a period of about 30 days. However, it has been observed that residual pulmonary obstruction at 6 months following the initial episode can independently predict the occurrence of recurrent venous thromboembolism and/or chronic thromboembolic pulmonary hypertension. This highlights the importance of monitoring and managing patients with persistent obstruction to prevent future complications (Aghayev & et al., 2016)

Differential Diagnosis

Differential diagnosis is a critical aspect of interpreting findings on imaging studies to ensure accurate diagnosis and appropriate management. Having awareness of potential differentials is crucial to avoid misdiagnosis and guide appropriate management decisions. Various factors and conditions can result in artifacts or simulate pulmonary emboli. These include pulmonary artery flow artifact, contrast-blood level due to slow flow, breathing motion, beam hardening, hyperconcentrated contrast in the superior vena cava, presence of medical devices, patient's arms positioned downward, and patient movement. Additionally, iatrogenic causes, neoplastic conditions, and inflammatory conditions should be considered in the differential diagnosis. Interpretational challenges may arise, such as misidentification of pulmonary veins as arteries or confusion at arterial bifurcations or branch points. These challenges can often be distinguished through multiplanar assessment. Being aware of these potential differentials is essential for accurate diagnosis and appropriate management of patients **(**Wittram & et al., 2004**);** (Hutchinson & et al., 2015).

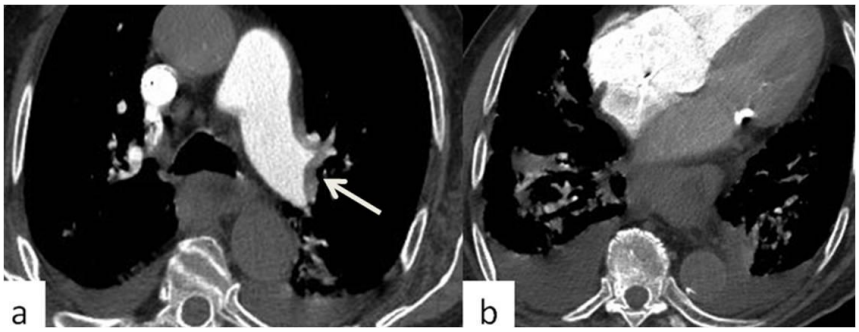

Figure3: In an 88-year-old male patient presenting with shortness of breath and a high clinical suspicion for emboli, a misleading arterial bifurcation point (a, arrow) is observed. The evaluation of pulmonary arterial segmental branches in the basal segments (b) is hindered by respiratory artifact.

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Emerging Technologies in Emergency Medicine: The Role of Artificial Intelligence and Robotics in Emergency Situations

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Introduction:

Emergency medicine is a specialized field that deals with the immediate assessment, diagnosis, and treatment of patients who require urgent medical care. As the demands on emergency departments continue to grow, healthcare professionals face numerous challenges and complexities. This chapter provides an overview of the current state of emergency medicine, highlighting the key challenges and the need for technological advancements to improve patient outcomes in emergency situations.

1. Overview of the Current State of Emergency Medicine

One of the primary challenges in emergency medicine is the constantly increasing patient load. Emergency departments often experience overcrowding, leading to delays in patient assessment, increased waiting times, and potential compromises in quality of care. The rise in patient load can be attributed to various factors, including population growth, aging populations, and limited access to primary care.

Emergency departments often face resource limitations, including staffing shortages, limited bed capacity, and equipment constraints. These limitations can hinder the ability to provide timely and efficient care to patients. The scarcity of resources further exacerbates the challenges in emergency medicine, making it crucial to explore innovative solutions to optimize resource utilization.

The Need for Technological Advancements in Emergencies

Emerging technologies, such as artificial intelligence (AI) and robotics, hold great promise in revolutionizing emergency medicine. These technologies have the potential to enhance decision-making, streamline processes, improve patient outcomes, and alleviate some of the challenges faced by emergency departments.

Artificial intelligence encompasses various techniques, including machine learning, natural language processing, and computer vision. In emergency medicine, AI can analyze large volumes of patient data, including electronic health records, vital signs, laboratory results, and imaging studies, to provide valuable insights for accurate and timely decision-making. AI-powered systems can assist in triage, diagnosis, risk prediction, and treatment recommendations, augmenting the capabilities of healthcare professionals.

Robotics offers innovative solutions for emergency medicine, enabling precise interventions and remote assistance. Robotic systems can assist in surgical procedures, telemedicine consultations, and emergency response. By leveraging robotics, healthcare

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providers can enhance their capabilities, perform complex procedures with greater precision, and provide timely interventions, particularly in challenging and high-stress situations.

2. Understanding Artificial Intelligence (AI) in Emergency Medicine

Explaining the Basics of AI and Its Applications in Healthcare

Artificial intelligence (AI) is a branch of computer science that focuses on developing intelligent systems capable of performing tasks that typically require human intelligence. In the context of healthcare, AI has the potential to revolutionize emergency medicine by improving decision-making, enhancing patient care, and optimizing resource allocation. This section provides an overview of the basics of AI and its applications in emergency medicine.

Definitions and Principles of AI

To understand AI in the context of emergency medicine, it is essential to define and understand the underlying principles of AI. AI encompasses various techniques, including machine learning, natural language processing, and computer vision. Machine learning algorithms enable computers to learn patterns from data and make predictions or decisions without being explicitly programmed. Natural language processing allows computers to understand and analyze human language, while computer vision enables the interpretation and understanding of visual information.

Applications of AI in Emergency Medicine

AI has a wide range of emergency medicine applications, providing healthcare professionals valuable tools and resources. One of the key applications is the development of decision support systems. These systems utilize AI algorithms to analyze patient data, medical literature, and treatment guidelines, providing real-time recommendations and alerts to assist emergency physicians in making accurate diagnoses and treatment plans.

Another important application of AI in emergency medicine is predictive analytics. By leveraging historical patient data, AI algorithms can identify patterns and predict outcomes, such as patient deterioration or the likelihood of developing complications. This predictive capability can assist emergency physicians in identifying high-risk patients, optimizing treatment decisions, and improving patient outcomes.

AI-Powered Triage Systems for Rapid Patient Assessment

Triage is a critical aspect of emergency medicine, aiming to prioritize patients based on the severity and urgency of their conditions. AI-powered triage systems have the potential to revolutionize the triage process, enabling rapid and accurate patient assessments.

Utilizing AI Algorithms in Triage Systems and the Benefits of AI-Powered Triage Systems

AI algorithms can analyze a wide range of patient data, including vital signs, symptoms, medical history, and demographic information, to prioritize cases based on their severity and urgency. By automatically processing and analyzing this information, AI-powered triage systems can assist healthcare professionals in making well-informed decisions and allocating resources efficiently.

The implementation of AI-powered triage systems offers several benefits in emergency medicine. Firstly, these systems can improve the accuracy and efficiency of patient

assessments, ensuring that critical cases receive prompt care. Secondly, AI algorithms can reduce waiting times, optimize resource allocation, and enhance the overall flow of patients through the emergency department. Lastly, AI-powered triage systems have the potential to improve patient satisfaction by streamlining the triage process and providing timely care.

Predictive Analytics and Machine Learning in Emergency Medicine

Predictive analytics and machine learning techniques are crucial in emergency medicine, enabling healthcare professionals to make informed decisions based on data-driven insights.

Leveraging Historical Patient Data

Emergency medicine generates vast amounts of data, including electronic health records, laboratory results, imaging studies, and real-time monitoring data. By leveraging machine learning algorithms, emergency physicians can analyze this data to identify patterns, predict outcomes, and assist in treatment decisions.

Identifying High-Risk Patients and Optimizing Treatment Decisions

The use of predictive analytics and machine learning in emergency medicine can help identify high-risk patients who may require immediate interventions or intensive care. By analyzing patient data and applying predictive models, healthcare professionals can tailor treatment plans, initiate appropriate interventions, and optimize resource allocation to achieve the best possible outcomes.

Conclusion: This chapter provides an in-depth understanding of artificial intelligence (AI) in emergency medicine, starting with an explanation of the basics of AI and its applications in healthcare. It highlights the definitions and principles of AI, including machine learning, natural language processing, and computer vision. The chapter then focuses on the applications of AI in emergency medicine, specifically decision support systems and predictive analytics. It explores how AI-powered triage systems can revolutionize rapid patient assessment, and how predictive analytics and machine learning can leverage historical patient data to predict outcomes and optimize treatment decisions. These AI-driven advancements have the potential to significantly enhance emergency medicine, improve patient outcomes, and support healthcare professionals in providing timely and accurate care in emergency situations.

3. Robotics in Emergency Situations

Introduction to Robotic Systems in Healthcare

The field of robotics offers immense potential in revolutionizing emergency medicine. This section provides an introduction to robotic systems in healthcare and explores their potential applications in emergency situations.

Potential Applications of Robotics in Emergency Medicine

Robotic systems have the capability to enhance patient care and improve outcomes in emergency medicine. They can be utilized in various domains, including surgical procedures, telemedicine, and assistance to healthcare professionals. This section highlights the potential applications of robotics in emergency medicine.

One of the significant applications of robotics is in surgical procedures. Surgical robots can assist surgeons in performing complex procedures with enhanced precision and minimal invasiveness. These robots provide improved visualization, dexterity, and stability, allowing surgeons to operate with high accuracy and control.

Another potential application is the use of telemedicine robots in emergency situations. These robots enable remote consultations, real-time collaboration between healthcare professionals, and expert guidance. They facilitate access to specialized care, particularly in remote or underserved areas, where immediate medical expertise may be limited.

Additionally, assistive robots can be employed in emergency medicine to aid healthcare professionals in tasks such as lifting, transferring patients, and providing physical support. These robots can help alleviate the physical strain on healthcare workers and improve patient care.

Robot-Assisted Surgeries and Interventions in Emergencies

Robot-assisted surgeries have gained significant attention in emergency medicine due to their potential benefits in performing complex procedures with precision and minimal invasiveness. Robotic systems offer several advantages in emergency surgical interventions. They provide enhanced visualization through high-definition cameras, allowing surgeons to navigate anatomical structures more accurately. The robotic arms' articulation enables precise movements and improved dexterity, reducing the risk of errors during critical procedures. Additionally, robot-assisted surgeries can result in smaller incisions, reduced blood loss, faster recovery times, and shorter hospital stays.

The use of robotics in emergencies can also minimize the exposure of healthcare professionals to potentially infectious or hazardous environments. Remote-controlled robotic systems can be utilized in situations where direct physical contact may pose risks, such as in the management of highly contagious diseases or hazardous material incidents.

The advantages of surgeries assisted by robots are numerous. They allow for greater precision and accuracy during the procedure, leading to a reduced risk of complications. In addition, robot-assisted surgeries often result in smaller incisions, which can lead to faster recovery times and less scarring. Patients may also experience less pain and discomfort during and after the surgery. Overall, robot-assisted surgeries offer a safer and more effective option for patients in need of surgical intervention.

Telemedicine and Remote Assistance Using Robotic Platforms

Telemedicine and remote assistance play a crucial role in emergency medicine, especially in situations where immediate access to medical expertise is limited. Robotic platforms enable remote consultations, real-time collaboration, and expert guidance, improving patient care in emergency situations.

Enabling Remote Consultations

Robotic platforms equipped with audiovisual capabilities and advanced communication tools facilitate remote consultations between healthcare professionals and patients. These platforms enable real-time assessment, diagnosis, and treatment recommendations, bridging the gap between patients and healthcare providers in emergency situations. Remote consultations can significantly improve patient outcomes, especially in cases where time-sensitive decisions are crucial.

Real-Time Collaboration and Expert Guidance

Robotic platforms allow healthcare professionals to collaborate in real-time, even when they are geographically distant. Experts can provide guidance and support to on-site medical teams during emergency procedures through these platforms. Real-time collaboration enhances

decision-making, improves patient outcomes, and ensures access to specialized expertise, regardless of geographical barriers.

This chapter explores the role of robotics in emergency situations, showcasing their potential applications in healthcare. The introduction to robotic systems highlights their potential in surgical procedures, telemedicine, and assistance to healthcare professionals. It emphasizes the benefits of robot-assisted surgeries, including enhanced precision, minimal invasiveness, and improved patient outcomes. Additionally, the chapter delves into the significance of telemedicine and remote assistance using robotic platforms, enabling remote consultations, real-time collaboration, and expert guidance in emergency situations. These advancements in robotics have the potential to revolutionize emergency medicine, improving patient care and outcomes.

4. Innovations in Pre-Hospital Care

Smart Ambulances Equipped with AI and Robotic Technologies

Integrating AI and robotics in ambulances can transform pre-hospital care by enhancing resource allocation, decision-making, and patient outcomes.

Smart ambulances equipped with AI and robotic technologies offer innovative solutions to improve pre-hospital care. These ambulances incorporate advanced sensors, AI algorithms, and robotic systems to optimize various aspects of emergency medical services.

One significant application is the utilization of AI algorithms in resource allocation and decision-making. These algorithms analyze real-time data, including geographical information, traffic conditions, and patient information, to optimize the dispatch of emergency services. By leveraging AI, ambulances can reach the scene of emergencies more efficiently, reducing response times and ensuring timely interventions.

Robotic technologies within smart ambulances can assist paramedics in providing enhanced care. For example, robotic systems can support automated vital sign monitoring, perform basic procedures, and provide real-time data transmission to medical professionals. These capabilities enable paramedics to deliver more effective care and provide timely updates to emergency departments.

AI Algorithms for Dispatching Emergency Services Efficiently

Efficient dispatching of emergency services is crucial for timely response and improved patient outcomes. AI algorithms play a significant role in optimizing resource allocation, response times, and routing efficiency in emergency dispatch.

Analyzing Real-Time Data for Efficient Emergency Service Dispatch

AI algorithms can analyze a wealth of real-time data to improve the efficiency of emergency service dispatch. These algorithms consider factors such as geographical information, traffic conditions, and patient information to make data-driven decisions. By dynamically assessing the urgency and severity of each case, AI algorithms can prioritize and dispatch emergency services more efficiently, ensuring that critical cases receive prompt attention.

The integration of AI algorithms in dispatch systems also improves resource allocation. By considering factors such as the availability of nearby healthcare facilities, specialized equipment, and personnel expertise, these algorithms ensure optimal utilization of resources,

including ambulances, medical personnel, and equipment. This optimization leads to improved response times and better allocation of healthcare resources.

Remote Monitoring and Diagnostic Tools for Paramedics

AI and robotic technologies can equip paramedics with advanced monitoring and diagnostic tools, enhancing their capabilities for remote assessment and early interventions.

Advancements in Remote Monitoring for Paramedics

Remote monitoring tools, integrated with AI and robotic technologies, enable paramedics to perform advanced monitoring in pre-hospital settings. Wearable devices, sensors, and AI algorithms enable real-time monitoring of vital signs, transmission of data to medical professionals, and early detection of critical conditions. Paramedics can leverage these tools to assess and monitor patients remotely, facilitating timely interventions and potentially preventing deterioration.

Furthermore, AI-powered diagnostic tools enhance paramedics' ability to make accurate emergency assessments. These tools analyze patient data, including vital signs, symptoms, and medical history, and provide real-time insights and recommendations. By leveraging AI and robotics, paramedics can access additional decision support and improve the accuracy of their assessments, leading to more effective treatment decisions.

Conclusion: This chapter explores the innovations in pre-hospital care through the integration of AI and robotics. Smart ambulances equipped with AI and robotic technologies optimize resource allocation, enhance decision-making, and improve patient care. AI algorithms for dispatching emergency services efficiently consider real-time data to improve response times and resource allocation. Remote monitoring and diagnostic tools, empowered by AI and robotics, enable paramedics to provide advanced care and make accurate assessments remotely. These innovations hold great potential for transforming pre-hospital care and improving patient outcomes.

5. Enhancing Emergency Room Efficiency with Technology

AI-Driven Decision Support Systems for Emergency Physicians

AI-driven decision support systems offer valuable tools for emergency physicians, providing real-time recommendations and alerts to enhance decision-making and improve patient care.

Implementing AI Algorithms for Real-Time Decision Support

The integration of AI algorithms in emergency medicine enables the development of decision support systems that analyze patient data, medical literature, and treatment guidelines to provide evidence-based recommendations to emergency physicians. These AI systems can process large amounts of data, including electronic health records, imaging results, and real-time monitoring, to aid in diagnosis, treatment planning, and clinical decision-making.

By leveraging machine learning, natural language processing, and computer vision techniques, AI-driven decision support systems can assist emergency physicians in interpreting complex data, identifying patterns, and making accurate and timely decisions. These systems can also alert physicians to potential adverse events, drug interactions, or clinical guidelines that should be considered during patient care.

Implementing AI-driven decision support systems has significantly improved diagnostic accuracy, treatment outcomes, and patient safety. Physicians can benefit from the expertise and insights AI algorithms provide, leading to enhanced clinical decision-making and improved patient care.

Automation of Routine Tasks in the Emergency Department

The automation of routine tasks within the emergency department using AI and robotic systems streamlines administrative processes, improves efficiency, and optimizes workflow.

Streamlining Administrative Tasks with AI and Robotics

AI and robotic technologies can automate various administrative tasks in the emergency department, such as patient registration, documentation, inventory management, and medication administration. These technologies enable seamless integration with electronic health records, automated data entry, and intelligent data processing

Automating routine tasks reduces the administrative burden on healthcare professionals, allowing them to focus more on direct patient care. By eliminating manual data entry and paperwork, AI and robotic systems free up valuable time, enhance accuracy, and improve workflow efficiency. This automation also contributes to better patient flow, reduced waiting times, and increased overall operational efficiency within the emergency department.

Virtual Reality and Augmented Reality Applications in Training and Simulations

Virtual reality (VR) and augmented reality (AR) technologies offer immersive training environments and realistic simulations for emergency medicine, facilitating skill enhancement and decision-making capabilities.

Realistic Training Environments with VR and AR

VR and AR applications provide emergency physicians with realistic training environments where they can practice various emergency procedures, scenarios, and interventions. Through immersive simulations, physicians can gain hands-on experience, improve procedural skills, and enhance decision-making under high-pressure situations.

VR and AR technologies enable physicians to visualize complex anatomical structures, simulate emergency scenarios, and practice critical procedures in a safe and controlled environment. These training experiences enhance skills, boost confidence, and reduce medical errors during real-life emergency situations.

Additionally, VR and AR can support collaborative learning and remote training by facilitating virtual interactions, team-based simulations, and knowledge sharing among emergency physicians and healthcare professionals.

AI-driven decision support systems provide real-time recommendations and alerts, empowering emergency physicians with valuable insights for improved decision-making. The automation of routine tasks in the emergency department through AI and robotic systems streamlines administrative processes and optimizes workflow. VR and AR applications create realistic training environments, enabling emergency physicians to enhance their skills, simulate emergency scenarios, and make better decisions under pressure.

By integrating these technological advancements into emergency medicine, healthcare institutions can achieve improved patient care, increased operational efficiency, and enhanced physician performance.

6. Ethical and Legal Considerations

Addressing Concerns about Privacy and Data Security

The integration of AI and robotics in emergency medicine raises concerns about privacy and data security. It is crucial to address these concerns to ensure the responsible use of technology and protect patient information.

Privacy Risks and Data Breaches

The utilization of AI and robotics involves the collection, storage, and analysis of vast amounts of patient data. This raises the risk of unauthorized access, data breaches, and potential misuse of sensitive information. Privacy risks may include the exposure of personal health information, loss of confidentiality, and threats to patient autonomy.

Healthcare institutions must implement robust security measures, encryption protocols, and strict access controls to mitigate these risks. This includes adopting secure data storage systems, conducting regular security audits, and providing training on data protection for healthcare professionals and staff. Compliance with relevant privacy laws and regulations, such as the General Data Protection Regulation (GDPR) or Health Insurance Portability and Accountability Act (HIPAA), is crucial to safeguard patient privacy.

Ensuring Transparency and Accountability in AI and Robotics

Transparency and accountability are essential factors in the deployment of AI and robotics in emergency medicine. It is crucial to ensure that algorithmic decision-making processes are transparent, accountable, and free from biases or errors.

Transparency in Algorithmic Decision-Making

The black-box nature of AI algorithms can raise concerns regarding their decision-making processes. To address this, efforts should be made to enhance the transparency of AI systems. This includes documenting the development process, data sources, and algorithmic models used in emergency medicine applications. Transparent AI systems enable healthcare professionals to understand and interpret the recommendations or predictions provided, fostering trust and facilitating effective collaboration between humans and machines.

Rigorous Testing and Validation

To ensure the reliability and safety of AI and robotic technologies, rigorous testing and validation processes are necessary. It is important to evaluate AI algorithms' performance, accuracy, and generalizability in emergency medicine scenarios. This can be achieved through rigorous clinical trials, comparative studies, and continuous monitoring of algorithm performance.

Regular auditing and evaluation of AI systems are essential to identify and rectify any biases, errors, or limitations. Validation processes should involve multidisciplinary teams, including healthcare professionals, technology experts, ethicists, and regulatory authorities, to ensure comprehensive scrutiny of the technology's capabilities and limitations.

Ethical Guidelines for the Use of Emerging Technologies in Emergencies

The responsible use of emerging technologies in emergencies necessitates the establishment of ethical guidelines to guide decision-making, protect patient rights, and promote ethical practices.

Establishing Ethical Principles

Ethical guidelines should encompass principles such as beneficence, non-maleficence, autonomy, and justice. These principles guide the responsible use of AI and robotics, ensuring that patient well-being, safety, and rights are prioritized. Ethical frameworks provide guidance for obtaining informed consent, maintaining patient privacy and confidentiality, and ensuring equitable access to emerging technologies.

Interdisciplinary collaborations involving healthcare professionals, technology developers, ethicists, and regulatory bodies are crucial for developing and updating ethical guidelines. Continuous evaluation and adaptation of ethical principles to emerging technologies and changing societal contexts are essential to ensure their relevance and effectiveness.

7. Case Studies and Real-World Examples

7.1 Showcasing Successful Implementations of AI and Robotics in Emergency Medicine

This section presents case studies that highlight the successful integration of AI and robotics in emergency medicine. These case studies demonstrate the practical applications of these technologies and their impact on patient care and operational efficiency.

Case Study 1: AI-Powered Triage System Implementation

In a large urban hospital, an AI-powered triage system was implemented to improve the efficiency and accuracy of patient assessment in the emergency department. The system utilized AI algorithms to analyze real-time patient data, including vital signs, symptoms, and medical history. By prioritizing cases based on severity and urgency, the system reduced wait times and ensured that critical patients received prompt care. The implementation resulted in a significant reduction in patient overcrowding, improved resource allocation, and enhanced patient satisfaction.

Case Study 2: Robot-Assisted Emergency Surgeries

A medical center introduced robot-assisted surgeries in their emergency department to address complex cases requiring surgical intervention. Using robotic systems, surgeons were able to perform minimally invasive procedures with enhanced precision and dexterity. The integration of robotics improved patient safety by reducing the risk of complications and minimizing surgical invasiveness. Additionally, the robot-assisted approach enabled faster recovery times, shortened hospital stays, and improved overall patient outcomes.

7.2 Highlighting Specific Cases Where Technology Made a Significant Impact

This section discusses specific real-world examples where AI and robotics have made a significant impact in emergency medicine, resulting in improved patient care and treatment effectiveness.

Case Study 1: AI-Based Predictive Analytics for Early Sepsis Detection

In a busy emergency department, an AI-based predictive analytics system was implemented to detect early signs of sepsis in patients. The system analyzed a wide range of patient data, including vital signs, laboratory results, and clinical notes, to identify patterns indicative of sepsis development. Through early detection and timely interventions, the system significantly reduced sepsis-related mortality rates, improved patient outcomes, and optimized the utilization of healthcare resources.

Case Study 2: Virtual Reality Simulation Training for Emergency Procedures

A training program was developed using virtual reality (VR) simulations to train emergency physicians in critical procedures such as airway management, cardiac resuscitation, and trauma management. The VR simulations provided a realistic and immersive environment for practicing these procedures, allowing physicians to gain confidence and improve their skills in a safe and controlled setting. As a result, emergency physicians demonstrated enhanced performance, increased speed, and improved decision-making during actual emergency situations.

These case studies showcase the tangible benefits of incorporating AI and robotics in emergency medicine. They demonstrate how these technologies can improve patient outcomes, reduce complications, enhance operational efficiency, and contribute to overall healthcare quality.

8. Future Perspectives and Challenges

Discussing Potential Future Advancements in AI and Robotics

This section explores the potential future advancements in AI and robotics that have the potential to shape the field of emergency medicine. It delves into emerging trends, technologies, and research directions that can further enhance patient care and outcomes.

Future Advancement 1: Intelligent Decision Support Systems

As AI continues to evolve, future advancements may include more sophisticated decision support systems that can analyze complex patient data, genetic information, and real-time monitoring data to provide personalized treatment recommendations. These systems may utilize advanced machine learning algorithms and deep learning techniques to improve diagnostic accuracy and treatment outcomes.

Future Advancement 2: Advanced Robotics and Automation

The future of robotics in emergency medicine may involve the development of more advanced robotic systems capable of performing complex surgeries with greater precision, autonomy, and adaptability. Additionally, automation may further streamline routine tasks in the emergency department, freeing up healthcare professionals to focus on critical patient care.

Overcoming Barriers to Widespread Adoption of Emerging Technologies

This section addresses the barriers that need to be overcome for the widespread adoption of emerging technologies, such as AI and robotics, in emergency medicine. It discusses factors such as cost concerns, regulatory frameworks, and workforce readiness.

Barrier 1: Cost and Affordability

The implementation of AI and robotic technologies can be costly, making it challenging for smaller healthcare institutions to adopt these advancements. Future efforts should focus on improving cost-effectiveness, developing scalable solutions, and exploring potential funding sources to make these technologies more accessible.

Barrier 2: Regulatory and Legal Considerations

The integration of AI and robotics in emergency medicine requires careful consideration of regulatory frameworks and legal implications. Clear guidelines, standards, and regulations

should be established to ensure patient safety, data privacy, and ethical use of these technologies.

Barrier 3: Workforce Readiness and Training

The successful adoption of AI and robotics in emergency medicine requires a workforce that is trained and ready to leverage these technologies effectively. Education and training programs should be developed to upskill healthcare professionals and equip them with the necessary knowledge and competencies to utilize these technologies in their practice.

Collaborations between Healthcare Providers and Technology Developers

This section emphasizes the importance of collaborations between healthcare providers and technology developers to drive innovation and successful implementation of AI and robotics in emergency medicine. It discusses the need for interdisciplinary partnerships, knowledge sharing, and ongoing dialogue to ensure that emerging technologies align with the needs and workflows of healthcare professionals.

Collaboration 1: User-Centered Design and Feedback

Healthcare providers should actively participate in the development and refinement of AI and robotic systems to ensure they address specific clinical needs, improve workflow efficiency, and align with user preferences. Regular feedback and iterative improvement processes can enhance the usability and effectiveness of these technologies.

Collaboration 2: Research and Development Partnerships

Collaborative efforts between healthcare institutions, academia, and technology companies can foster innovation and advance the field of AI and robotics in emergency medicine. By combining expertise, resources, and insights, these partnerships can drive research, validate new technologies, and facilitate the translation of research findings into real-world applications.

Conclusion

In conclusion, this chapter has provided a comprehensive overview of the role of artificial intelligence (AI) and robotics in emergency medicine. It has highlighted the current challenges faced in emergency medicine, including increasing patient loads and limited resources. The chapter has emphasized the need for technological advancements to overcome these challenges and improve patient outcomes.

The discussion on AI in emergency medicine has shed light on the basics of AI and its applications in healthcare. It has explored how AI can analyze large volumes of patient data to provide valuable insights for decision-making, assist in triage, and predict outcomes. AI-powered systems have the potential to revolutionize the way emergency physicians assess and prioritize patients, leading to more efficient and accurate care.

Additionally, the chapter has delved into the role of robotics in emergency medicine, showcasing how robotic systems can enable precise interventions, remote assistance, and improved surgical procedures. The integration of robotics in emergency medicine can enhance the capabilities of healthcare providers and improve patient outcomes, particularly in complex and high-stress situations.

Throughout the chapter, ethical and legal considerations have been highlighted, emphasizing the importance of privacy, transparency, and accountability when implementing

AI and robotics in emergency medicine. These considerations ensure responsible and ethical use of emerging technologies for the benefit of patients and healthcare providers.

Furthermore, the chapter has presented case studies and real-world examples to showcase the successful implementation and impact of AI and robotics in emergency medicine. These examples serve as evidence of the potential benefits and effectiveness of these technologies in improving patient care and operational efficiency.

Looking to the future, the chapter has discussed potential advancements, challenges, and the importance of collaborations between healthcare providers and technology developers. By addressing barriers to widespread adoption and fostering interdisciplinary partnerships, the full potential of AI and robotics in emergency medicine can be realized.

In summary, the integration of AI and robotics in emergency medicine offers tremendous opportunities to enhance decision-making, optimize resource utilization, and improve patient outcomes. By leveraging these emerging technologies responsibly and ethically, emergency medicine can benefit from increased efficiency, accuracy, and effectiveness in providing urgent medical care. It is essential for healthcare professionals, policymakers, and researchers to continue exploring and embracing these advancements to shape the future of emergency care positively.

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Hyponatremıa in the Emergency Department

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Introduction

Hyponatremia is defined as a serum sodium level <135 mmol/L and is seen in a substantial number of patients presenting to the emergency department. It usually presents with nonspecific symptoms. Symptoms such as recent fall history, vertigo, and weakness are some of them. Etiologic factors of hyponatremia include the syndrome of inappropriate ADH (SIAD), diuretics, and heart failure (HF). In the treatment of hyponatremia detected in the emergency department, firstly acute-chronic differentiation should be made and treatment options are organized according to symptomatic status. We aimed to present a comprehensive overview of the etiologic factors of hyponatremia, how they present to the emergency department, and treatment options.

Definiton

Hyponatremia is defined as a fall in serum sodium below the relevant laboratory threshold value, which may vary between institutions. It is most commonly defined as a fall in serum sodium below 135 mmol/L (Spasovski et al., 2014). Hyponatremia is the most common electrolyte disorder in clinical medicine (Kheetan et al., 2021). It affects approximately 10% of patients admitted to hospitals (Arampatzis et al., 2012). The mechanisms leading to hyponatremia are complex and cause confusion and misconceptions in physicians dealing with electrolyte disorders. The underlying mechanism should be well understood when designing treatment

The occurrence of symptoms is strongly correlated with the rate of development of hyponatremia. Classification of mild (130-135 mmol/L), moderate (125-129 mmol/L), and profound (<125 mmol/L) has been proposed (Spasovski et al., 2014). Emergency physicians should be aware that there may be significant differences in sodium levels between serum and whole blood (Solak, 2016).

Etiological factors

The prevalence of hyponatremia in patients presenting to the emergency department ranges from 3% to 10% (Arampatzis et al., 2012), (Olsson et al., 2013). In special patient populations, such as geriatric patients, hyponatremia is even more prevalent during ED presentation (Boyer et al., 2019). Possible reasons for the higher prevalence of hyponatremia in the elderly are the high number of daily medications, comorbidities, and decreased concentration/dilution ability of the kidneys in this population (Arampatzis et al., 2013), (Mannesse et al., 2013), (Filippatos et al., 2017). Furthermore, the prevalence of hyponatremia

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in patients presenting to the emergency department may vary seasonally: a higher prevalence is present during warmer periods when the intake of hypotonic fluids may increase, and it is more common in elderly patients(Pfortmueller et al., 2014), (Imai et al., 2018). In addition, it has been found that patients with acute or chronic kidney disease are significantly more likely to suffer from hyponatremia when presenting to the emergency department, with prevalence rates as high as 30% for those with acute-chronic kidney disease (Woitok et al., 2020).
Given this information, emergency physicians should be more strongly suspicious of hyponatremia in specific groups such as the elderly, patients taking diuretics, especially aldosterone-antagonists and thiazide and similar diuretics, or patients with acute-chronic kidney disease.

Pathogenesis

Serum sodium concentration

Serum sodium is determined by the total amount of exchangeable sodium and potassium and total body fluid, as can be seen in the Edelman equation (Edelman et al., 1958):

$$Na+ = (Na^{+\ \text{exchangeable}} + K^{+\ \text{exchangeable}}) / \text{Total body fluid}$$

It should be noted that there are osmotically inactive, non-exchangeable sodium stores in the body and these are not included in the formula (Rohrscheib et al., 2022). Potassium is included in the formula because the Edelman equation implies equal solute concentrations across cell membranes and sodium is the main extracellular and potassium the main intracellular solute. Since water can pass through cell walls, the solute concentration is equal in intracellular and extracellular fluids (Rohrscheib et al., 2022).

According to the Edelman equation, hyponatremia can only develop if there is a loss of sodium, a gain of water, or a combination of both. It can be concluded that an increase in total exchangeable potassium can affect the serum sodium concentration. This is important when treating a patient with both hyponatremia and hypokalemia in the emergency department. Potassium maintenance may lead to a higher correction of serum sodium. Hyponatremia can also be caused by a shift of free water from the intracellular to the extracellular space caused by any osmotically active substance. Hyperglycemia is the most important cause of this. It has been suggested that for every 5.6 mmol/L increase in serum glucose, serum sodium decreases by 1.6 mmol/L (Hillier et al., 1999).

Water Homeostasis

As expressed in the Edelman equation, serum sodium concentration is the result of the ratio of the amount of sodium to total body water (Edelman et al., 1958). Therefore, serum sodium reflects the state of water homeostasis. The development of thirst and the effects of anti-diuretic hormone (ADH) is essential for the regulation of body water (Spasovski et al., 2014). ADH is secreted when plasma osmolality rises above approximately 285 mosm/kg and thirst develops at slightly higher values (Verbalis, 2003), (Robertson et al., 1973). As a result, water is absorbed from aquaporins, which are water-conducting channels in the collecting duct of the kidney, via ADH. Thus, plasma osmolality will reach the normal range again. It is noteworthy that ADH secretion is also triggered by stretch-sensitive baroreceptors: Even small decreases in blood pressure can lead to increased ADH secretion (Baylis, 1983). In more severe hypovolemia, baroregulation may override osmoregulation, leading to ADH secretion despite marked hypoosmolarity (Robertson, 1983).

Classification of hyponatremıa

Since the most common form of hyponatremia seen clinically is hypotonic, we prefer to classify hyponatremia according to volume status. The limitations and challenges of this approach are summarized below.

Determination of volume status

Volume depletion, defined by sodium (and fluid) loss, occurs through bleeding, and gastrointestinal or renal losses and should be distinguished from dehydration, which is caused by water loss and is usually accompanied by hypernatremia and associated hyperosmolarity (McGee et al., 1999). It is important to distinguish between these two conditions because dehydration is mainly addressed by free water replacement, whereas volume depletion should be treated by the administration of isotonic crystalloids (Lindner & Funk, 2013).

Clinical signs of hypovolemia include severe postural dizziness, a postural increase in pulse rate exceeding 30 beats/min, a dry axilla, dry mucous membranes, and a chapped tongue (McGee et al., 1999). Skin turgor and capillary refill time have no proven diagnostic value in assessing volume status in adults (McGee et al., 1999).

Laboratory parameters such as serum creatinine, urea, or hemoglobin indicate the presence of dehydration or hypovolemia but should be interpreted with caution and only if baseline values are available.

Ultrasound alone or in combination with passive leg raising is recommended to assess volume status. Ultrasound is usually used to determine the diameter and collapsibility of large veins (Pourmand et al., 2019). Taken together, the emergency physician needs to assess volume status by combining different tests. Clinical findings should be combined with laboratory parameters and ultrasonographic evaluation of the great vessels. However, it should be remembered that volume status is difficult to determine, the methods used to do so are controversial and reported sensitivities and specificities are low, which may lead to misinterpretations (Spasovski et al., 2014).

Hypovolemic hyponatremia

Various mechanisms cause volume depletion, ADH secretion, and consequently hyponatremia. Diuretics are the leading cause of hyponatremia (Arampatzis et al., 2013). Diuretic-associated renal sodium loss may cause mild hypovolemia and thus ADH release. Substitution of hypotonic fluid for the lost fluid leads to the development of hyponatremia. Thiazide and thiazide-like diuretics directly cause hyponatremia (Spasovski et al., 2014). Thiazides may impair free water excretion through volume-dependent ADH release, decreased distal conduction, inhibition of thiazide-sensitive sodium chloride cotransporter (NCC) impairing maximal urine dilution, and increased collecting duct permeability (Filippone et al., 2020). Advanced age and female gender are important risk factors for the development of hyponatremia in patients taking thiazides, while low body mass index is controversial as a risk factor (Barber et al., 2015; Rodenburg et al., 2013). Therefore, it is very important to carefully evaluate the current medications of patients with hyponatremia in the emergency department, because thiazide (and similar) diuretics are often found in combinations of antihypertensive drugs.

Gastrointestinal sodium loss can occur through severe diarrhea. Furthermore, severe vomiting triggers renal sodium loss to counteract metabolic alkalosis because sodium must be excreted in the urine along with bicarbonate (Spasovski et al., 2014). Sodium can also be lost in significant amounts through the skin as a result of excessive sweating. In addition to

cutaneous sodium losses, excessive drinking of hypotonic fluids also plays an important role (Hew-Butler et al., 2017; Seal et al., 2019). Adrenal insufficiency can lead to hyponatremia, both primary and secondary, due to sodium loss triggered by hypovolemia and decreased aldosterone activity (Kobayashi et al., 2013; Spital, 1982). Patients with glucocorticoid deficiency may have increased ADH levels (Kamoi et al., 1993). Kidney disease can cause renal salt loss. Renal salt loss is characterized by polyuria, hypovolemia, and hyponatremia (Hamdi et al., 2010).

Cerebral salt loss is characterized by hypovolemia, hyponatremia, and polyuria, similar to renal salt loss, but usually occurs as a result of intracranial pathologies, trauma, or surgery (Leonard et al., 2015). The mechanisms underlying cerebral salt loss are not fully understood. Treatment consists of fluid and sodium replacement to maintain volume status and sodium within physiologic limits (Leonard et al., 2015).

Hypervolemic hyponatremia

The prevalence of hyponatremia in patients with heart failure is approximately 25% (Dunlap et al., 2017; Lee et al., 2018; Omar et al., 2017). Furthermore, hyponatremia on admission has been independently associated with unfavorable outcome and correction of serum sodium has proven to be beneficial for outcome (Wang et al., 2019). In heart failure, decreased effective circulating volume and retention of free water triggering non-osmotic ADH release leads to hyponatremia, while activation of the renin-angiotensin-aldosterone system leads to sodium retention (Spasovski et al., 2014). Furthermore, angiotensin II leads to increased thirst through osmoreceptor stimulation (Fitzsimons, 1998). Therefore, hyponatremia is a consequence of increased thirst and consequent ADH-induced fluid retention. In total, hyponatremia occurs because water retention is more dominant than sodium retention.

Liver cirrhosis is another common cause of hyponatremia: Splanchnic vasodilatation and consequent activation of the renin-angiotensin-aldosterone system, together with the release of ADH to compensate for the lower effective circulating volume, ultimately leads to hyponatremia (Alukal et al., 2020).

In patients with nephrotic syndrome, the effective circulating volume may be reduced due to decreased oncotic pressure as a result of renal protein loss. As in heart failure and liver cirrhosis, activation of the renin-angiotensin-aldosterone system and non-osmotic release of ADH results in edema and hyponatremia (Palmer & Alpern, 1997).

Normovolemic hyponatremia

The syndrome of inappropriate ADH secretion (SIADH) is characterized by a non-osmotic and non-volume-based release of ADH by the pituitary gland or through ectopic production [3]. Mutations of the vasopressin V2 receptor have been described to cause SIADH, which is usually associated with low levels of circulating ADH (Rosenthal et al., 2006; Tong et al., 2021). In SIADH, free water is retained and urine concentrates to a relatively hyperosmolar state. Therefore, the first diagnostic criterion for SIADH is Urine osmolality >100 mosmol/kg, but often >300 mosmol/kg. On the one hand, hyponatremia in SIADH is caused by the retention of free water through excessive ADH secretion (or increased activity or mutation of the vasopressin V2 receptor) (Spasovski et al., 2014). On the other hand, an increase in circulating effective volume triggers natriuresis. The second diagnostic criterion for SIAD: Urine sodium >40 mmol/L. Additional criteria include decreased effective serum osmolality, clinical euvolemia, absence of diuretic use, and absence of thyroid, adrenal, pituitary or related renal insufficiency (Ellison & Berl, 2007). SIAD is difficult to diagnose for several reasons: Determination of volume status is difficult and controversial as mentioned above. For the

emergency physician, it is crucial to identify patients with potential SIAD to reduce the risk of further drops in serum sodium due to fluid administration. A wide range of diseases, especially malignancy and pulmonary diseases, medications, and symptoms such as pain or nausea can trigger SIAD (Ellison & Berl, 2007). In transient SIAD, for example, after experiencing severe pain, the triggering condition may have disappeared by the time of admission. However, in some cases of SIAD, no specific cause can be identified. Hypothyroidism is another rare cause of hyponatremia and is usually only seen in cases of significant thyroid dysfunction where TSH levels are significantly increased (Schwarz et al., 2012; Spasovski et al., 2014).

Symptoms of hyponatremia

Symptoms attributable to hyponatremia range from mild, non-specific syndromes to severe, life-threatening brain edema (Spasovski et al., 2014). In general, the severity of symptoms is linked to the speed of hyponatremia development (Lindner & Schwarz, 2012). The faster hyponatremia develops, the shorter the time for the brain to adapt to the new hypoosmolar environment by reducing its intracellular osmotically active particles (Adrogué & Madias, 2000). These "regulatory volume depletion" mechanisms act through rapid compensatory pathways, such as the influx of water from the brain parenchyma into the cerebrospinal fluid and the removal of electrolytes from the intracellular space to the extracellular space (Gankam Kengne & Decaux, 2018). These mechanisms can compensate for acute hyponatremia to a limited extent. Brain cells can lose at most 20% of their intracellular electrolytes to compensate for the hypoosmolar environment (Gankam Kengne & Decaux, 2018). Therefore, deeper acute hyponatremia leads to significant brain edema and ultimately death. On the other hand, slowly developing hyponatremia can be compensated by a late adaptation to hypoosmolality through the reduction of organic osmolytes in brain cells, which account for about 30% of intracellular osmolytes, even when serum sodium reaches levels around 100 mmol/L (Sterns, 1990).

The difference in compensatory mechanisms occurring acutely (i.e. excretion of intracellular electrolytes) and slowly (reduction of intracellular osmolytes) requires physicians to distinguish between acute and non-acute hyponatremia to guide initial treatment.

In a retrospective analysis in a large emergency department, nausea, a history of falls, weakness, and dizziness were the most common symptoms attributable to hyponatremia (Arampatzis et al., 2012). Confusion, headache, seizures, and syncope have also been reported in patients with hyponatremia (Arampatzis et al., 2012). There is increasing evidence that hyponatremia also triggers osteoporosis (Barsony et al., 2019), leads to an increased risk of fractures even independently of osteoporosis (Kinsella et al., 2010), and is an independent risk factor for falls [64]. Elderly patients are particularly vulnerable to this vicious cycle of adverse consequences of hyponatremia. (Boyer et al., 2019; Dokmak & Madias, 2019).

The emergency physician needs to be alert to potential hyponatremia when dealing with elderly patients presenting to the emergency department with non-specific complaints or falls. Furthermore, hyponatremia should be considered a differential diagnosis in all patients with non-specific complaints such as vertigo, headache, or nausea, especially in patients taking thiazide and similar diuretics, aldosterone-antagonists, or patients with malignancies.

Diagnosis of hyponatremia in the emergency department

After the detection of hyponatremia in the emergency patient, several diagnostic steps are required. It is crucial to take a thorough history focusing on current medications with particular attention to the onset of symptoms and combination antihypertensive agents including thiazide diuretics, corticosteroids, and psychotropic drugs. Symptoms associated with hyponatremia should be systematically assessed. Careful determination of volume status involving multiple

tests as outlined above is essential. A review of recent laboratory tests is important in differentiating acute hyponatremia from chronic hyponatremia. Glucose should be measured to rule out hyponatremia due to hyperglycemia, given that the reduction in serum sodium can vary significantly depending on body composition (Wolf, 2017). Also, the higher the blood glucose, the less the drop in serum sodium will be due to cellular dehydration. Since the feared consequences of hyponatremia, such as cerebral edema, depend on tonicity and not on absolute serum sodium level, hyperglycemia-induced hyponatremia does not require sodium correction, at least if it does not persist after blood glucose normalization (Adrogué & Madias, 2000). Potassium levels should be checked in hyponatremic patients on diuretics, as hypokalemia is a common concomitant finding (Ravioli et al., 2021). Serum osmolality, creatinine, urea, and TSH should also be determined. Serum cortisol levels should be requested in patients with suspected adrenal insufficiency. Urine sampling to analyze urine chemistry, including osmolality and sodium concentration, is crucial to assess the response to hyponatremia.

Management of hyponatremia in the emergency department

After ruling out hyponatremia due to hyperglycemia, the first step in the management of hyponatremia is to clarify whether the sodium disorder is symptomatic. The treating physician should make sure that the symptoms are not due to a different cause before starting treatment (Chifu et al., 2021).

Symptomatic hyponatremia

According to the European clinical practice guideline, acute hyponatremia with severe or moderately severe symptoms (i.e. onset <48 hours) should be treated immediately by infusion of 150 ml of 3% NaCl solution over 20 minutes followed by repeat measurement of serum sodium after 20 minutes (Spasovski et al., 2014). Moderately severe symptoms have been described as nausea with vomiting, confusion, and headache, while severe symptoms have been described as vomiting, cardiorespiratory distress, somnolence, coma, and seizures (Sterns, 1990). When administering 3% NaCl, a weight-based infusion approach (2 ml/kg body weight) can be applied. Slow and continuous administration of hypertonic saline did not differ in overcorrection rate compared to a rapid and intermittent bolus of 3% saline (Baek et al., 2021). In patients with symptomatic hyponatremia, the treatment goal is a rapid increase in serum sodium of 5 mmol/L. For this, 3% saline administration can be repeated. Serum sodium should be checked at least 6-12 hours after the resolution of symptoms and daily until normalization (Spasovski et al., 2014). In case of repeated 3% saline infusion, serum sodium should be checked more frequently (every 4 hours). In total, the maximum correction of serum sodium of 8-10 mmol/L/24 hours should not be exceeded (Spasovski et al., 2014).

Asymptomatic hyponatremia

In asymptomatic hyponatremia, it should be determined whether the fall in serum sodium has occurred acutely (<48 hours). Acute hyponatremia is a documented fall in serum sodium within the last 48 hours. The current practice guideline for hyponatremia recommends giving 150 ml of 3% saline (or 2 ml/kg body weight) within 20 minutes of a documented acute fall in serum sodium >10 mmol/L, followed by a recheck of serum sodium 4 hours later (Spasovski et al., 2014). In case of non-acute, asymptomatic hyponatremia in hypovolemic patients, e.g. diarrhea, dehydration with excessive diuretic therapy, etc., hydration should be initiated using isotonic crystalloids at a dose of 20 ml/kg/24 h (Lindner & Schwarz, 2012; Spasovski et al., 2014). In hypervolemic patients with non-acute, asymptomatic hyponatremia (e.g. heart failure or liver cirrhosis), fluid restriction should be initiated unless contraindicated (Spasovski et al.,

2014). The use of non-essential fluids, diuretics, i.e. thiazides and their analogs or potassium-sparing diuretics, should be avoided by the emergency physician.

In addition to the treatment of acute and symptomatic hyponatremia, initiating the correct diagnostic steps is the most important task of the emergency physician. In asymptomatic, non-hypovolemic patients with hyponatremia in the emergency department, it is not advisable to initiate treatment before diagnostic measurements are performed and interpreted to prevent worsening of hyponatremia, for example, because fluid administration in patients with underlying SIAD potentially worsens hyponatremia.

Overcorrection of hyponatremia

Overcorrection of hyponatremia is defined as an increase in serum sodium exceeding 8-10 mmol/L/24 hours (Spasovski et al., 2014). Risk factors for overcorrection include low baseline serum sodium, associated low serum potassium level, low body mass index, chronic alcohol use, presence of cancer, and severe symptoms attributable to hyponatremia (Kim et al., 2020; Woodfine et al., 2019; Yang et al., 2022). Patients with higher urine output after the start of treatment have an increased risk of overcorrection (Chifu et al., 2021). In the case of hypokalemia, concomitant potassium replacement can cause serum sodium levels to rise rapidly via sodium-potassium exchange by Na-K-ATPase (Yang et al., 2022). Therefore, patients with hypokalemia are prone to overcorrection and complications associated with the correction of hyponatremia (Berl & Rastegar, 2010; Yang et al., 2022). If overcorrection is confirmed, prompt measures should be taken to reduce serum sodium back below the target correction rate of 8-10 mmol/L/24 h (Spasovski et al., 2014). Rapid re-lowering of serum sodium after overcorrection may prevent the occurrence of osmotic demyelination syndrome, as shown in animal models and case reports (Gankam Kengne & Decaux, 2018; Ochiai & Uenishi, 2018). Desmopressin has proven effective in preventing or treating overcorrection of hyponatremia in a retrospective study (Perianayagam et al., 2008). Free water infusion in the form of dextrose-5 solutions (2-3 ml/kg/h) can be used in addition to desmopressin (2-4 μg every 6-8 hours) or alone to control the increase in serum sodium and even to reinitiate hyponatremia in case of overcorrection (Rondon-Berrios, 2020).

Complications

Osmotic demyelination syndrome is a potential complication of a very rapid increase in serum sodium (Adrogué & Madias, 2000). It is an expression of the inability of neuronal cells to adapt to rapid changes in tonicity (Voets et al., 2022). It occurs mostly during the overcorrection of hyponatremia, but the syndrome can also occur with rapid increases in serum sodium without preceding hyponatremia. Risk factors for the occurrence of osmotic demyelination syndrome include metabolic imbalances, liver disease, chronic alcoholism, malnutrition, pregnancy, severe illness, and adrenal insufficiency (Shah et al., 2018).

The most common symptom of osmotic demyelination syndrome is altered mental status (Fitts et al., 2021). However, the symptoms are very diverse. The diagnosis is based on clinical suspicion and confirmed by brain MRI, which may reveal lesions in the pons [84]. Treatment of osmotic demyelination syndrome includes plasmapheresis, immunoglobulin administration, and corticosteroids, although evidence is limited (Kalampokini et al., 2021).

Conclusion

Hyponatremia is a common electrolyte disorder in patients presenting to the emergency department. Common causes include hypovolemia, diuretics, heart failure, liver cirrhosis, and SIAD. Differentiating symptomatic hyponatremia from asymptomatic hyponatremia is crucial

to start adequate treatment and prevent complications. The diagnosis of hyponatremia requires clinical suspicion and laboratory evaluation. In asymptomatic patients, initiation of adequate diagnostic steps in the emergency department should be a priority, as treatment should be diagnostic. The points that should not be forgotten are the association of hypokalemia-hyponatremia, the association of hyponatremia-osteoporosis, the fact that it is more common in hot weather and that 3% NaCl infusion, which is often overlooked by physicians who do not follow the new guidelines, can now be performed for as short as 20 minutes.

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Behavıor Dısorders Observed In Cat

Emre AYDEMİR
Nilgün YAPICI

BEHAVIORS

Behavior is a response to certain stimuli. Normal and abnormal behaviors are exhibited as a result of the different reactions given by the stimulus or stimuli. On these displayed behaviors; both genetic and; It is known that environmental factors have an effect. In particular, while genetic factors affect species-specific behaviors; Environmental factors cause various behaviors to be exhibited. While these behaviors are exhibited normally under optimum conditions; It is observed that abnormal behavior is exhibited with the change of optimum conditions (Marti et al. 1994; Schoutten and Wiegant 1997; Carr 2002; Levine et al. 2005; Mormede 2005; Nelson 2006; Heath 2007; Wechsler and Lea 2007; Ellis 2009; Ellis and Wells 2010; Aydemir and Bilge 2022; Tekşam and Aydemir 2022).

(1)

ABNORMAL BEHAVIORS

It is also observed that the model animal exhibits some abnormal behaviors contrary to their normal behaviors due to various genetic and environmental reasons such as fear, different light wavelength, different sound frequencies, temperature, and stress (Marti et al. 1994;

Schoutten and Wiegant). 1997; Carr 2002; Sambraus 2002; Levine et al. 2005; Nelson 2006; Overall 2013; Aydemir and Bilge 2022; Aydemir and Tekşam 2022).

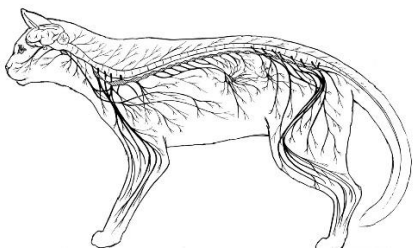
(2)

Aggression, environmentally harmful behaviors, wool (cloth) sucking, caprophagia, aggression, depression, anxiety, obsessive-compulsive disorder, sexual behavior disorders, maternal behavior disorders, pica syndrome, sexual disorders, and stress, as an indicator of the condition of the model animal. malnutrition and various sleep problems are observed (Marti et al. 1994; Schoutten and Wiegant 1997; Carr 2002; Levine et al. 2005; Nelson 2006; Ellis 2009; Overall 2013; Aydemir and Bilge 2022; Aydemir and Tekşam 2022).

CAUSES OF ABNORMAL BEHAVIORS

Abnormal behavior in the model animal generally varies depending on genetic and environmental factors. It is known that environmental factors rather than genetic factors affect abnormal behaviors (Marti et al. 1994; Schoutten and Wiegant 1997; Carr 2002; Levine et al. 2005; Meaney et al. 2007; Aydemir and Bilge 2022).

The sex of the model animal, age, psychological state, physiological and chemical structure, care and shelter conditions, stress, and similar factors are among the main factors (Marti et al. 1994; Schoutten and Wiegant 1997; Carr 2002; Levine et al. 2005; Meaney et al. 2007; Amat et al. 2015; Aydemir and Bilge 2022).



(3)

OBSERVED ABNORMAL BEHAVIORS

Agresyon

Cats can act aggressively when they feel threatened or forced into something they don't want. Many factors cause this behavior. Generally; can perform instinctively for mating, hunting, pain, protection, and defense of its young or territory (Mormede 2005; Wechsler and Lea 2007; Hart et al. 2014.

(4)

This behavior can be seen as attacking other cats in a social environment, raising the hair on the spine, identifying their places with urine, excessive possession and scratching, as well as fear of other cats, hiding in nooks by shrinking themselves and stinging. Moreover; aggression towards people is usually for play or manipulation (Mc et al. 1988; Landsberg et al. 2003; Mormede 2005; Wechsler and Lea 2007; Hart et al. 2014).

(5)

Depression

It is a type of depressive mood state observed in cats. Generally; shedding, being indifferent to stimuli, urinary incontinence in stressful situations, or urinating in a different place, the desire to escape, high body temperature, the cat licking itself and its surroundings, excessive salivation, eating disorder, desire to sleep, excessive fear and avoiding the crowd is the most obvious situations. (Mc et al. 1988 Landsberg et al. 2003; Mormede 2005; Wechsler and Lea 2007; Amat et al. 2015).

Mental Disorder

It is a situation where the mother cat does not own her kitten and rejects it. Basically, the mother cat, who does not accept her pregnancy and her kitten, refuses to nest and breastfeed her kitten after birth, does not care, and even abandons the kitten (Marti et al. 1994; Schoutten and Wiegant 1997; Carr 2002; Levine et al. 2005; Mormede 2005; Wechsler). and Lea 2007; Hart et al. 2014; Amat et al. 2015; Aydemir and Bilge 2022).

(6)

Pica Syndrome

Pica syndrome is not a psychologically based behavior disorder, but can also be caused by a cat's physical disorders such as anemia, liver disease, vitamin and mineral deficiency, skin disease, chronic pain, fleas, lice, central nervous system diseases, hearing loss, and thyroid. Cats with pica syndrome generally tend to eat string (wool), wire, plastic, tape, fabric, cat litter, needles, and soil. Moods such as stress, anxiety, depression, violence, and early weaning are among the causes of this behavior disorder. Behaviorally; pacing, excessive licking and cleaning, and meowing without any reason are observed (Hart et al. 2014; Amat et al. 2015).

(7)

Mating Behavior Problems

Behavioral disorders are frequently seen in cats due to anger. Among the most common behaviors are urination and loud meowing to mate, to tend to the surrounding objects, to the owner's leg, or to leave an odor to the opposite sex (Smith and Jansen 1977; Amat et al. 2015). Despite that; avoidance of mating, lack of desire for the opposite sex, and a lifestyle isolated from other cats can also be seen. This condition is often associated with anxiety.

(8)

Stress Related Situations

This behavior generally occurs as a result of stress factors such as losing the owner, change of caregiver, being loved by strangers, being bullied especially by young children, changing the place where he has lived for a long time, and restricted access to the toilet (Hart et al. 2014).

Obsessive Compulsive Disorder

Intense anxiety and stress cause anxiety, and anxiety causes obsessive-compulsive disorders. The model animal wants to do the same things over and over. If it does not, the model animal becomes aggressive. Behaviorally; is observed that they exhibit behaviors such as chasing their tail, meowing with a constant tone of voice, and regularly gnawing and scratching the same objects (Hart et al. 2014; Amat et al. 2015).

(9)

Urine Marking

If the cat is constantly spraying urine, this is abnormal behavior. It is known that this event is mostly caused by stress. When it is done to protect the area, is seen as normal behavior. In addition, it is stated that the behavior increases with the increase in the number of cats in the house and the addition of foreign cats and people to the house.

(10)

Urinating Or Defecating Outside The Designated Place

This behavior is when the model animal urinates or defecates outside of a specific toilet area. There is a difference between urine sprayed for field marking purposes and normal urination of the model animal.

(11)

In the normal urination behavior, cats release large amounts of urine with the squatting posture; marking behavior with urine is the release of very small amounts. The determined urination or defecation behavior can be caused by many reasons such as health problems, problems with the toilet bowl, stress.

Wool (Fabric) Suction

Wool-sucking behavior includes sucking and chewing different materials such as fabric and plastic as well as absorbing wool. Early weaning, separation anxiety, and faulty feeding methods are among the factors that have been suggested to contribute to the development of wool-sucking behavior (Aydemir and Bilge 2022).

(12)

Anxity

It is an abnormal behavior disorder that occurs as a result of the model animal feeling in danger. With this behavior disorder, it has been observed that the model animal generally becomes aggressive as a result of excessive anxiety and worry (Amat et al. 2015).

(13)

In addition, there are symptoms such as heart palpitations, rapid breathing, tremors, vomiting and diarrhea, and especially pupillary mydriasis in cats, shedding, urinary incontinence. Anxiety is considered to have become chronic in cases where it continues after the stressor that causes anxiety has disappeared. The model animal may exhibit various behaviors such as itching, depression symptoms, and aggression when it is anxious.

Sexual Behavior Disorders

It is the state of having little or no sexual interest in the model animal. Various behavioral disorders are observed due to factors such as malnutrition, isolated lifestyle, and the asocial mood of the model animal.

Moreover; It is seen that taking male cats to the female for mating will damage the sense of hierarchy in the male cat and cause sexual reluctance again.

(14)

Due to excessive sexual desire, she may show sexual intimacy towards furniture and human legs, kittens, other animals, and various objects. On the other hand, the female cat's inability to mate during the heat period is a source of stress, and there are always aggressive, aggressive, etc. appear to have behavioral disorders.

(15)

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The Effects Of Extremely Low Frequency Electromagnetıc Fıelds On Cellular Homeostasıs

Figen ÇİÇEK[1]

INTRODUCTION

All living things are constantly exposed to electromagnetic radiation from the sun throughout their lives. In addition, life goes on in the presence of the earth's natural electromagnetic field. Today, in addition to these natural electromagnetic fields (MF), modern life continues in the presence of magnetic fields induced by electrical currents.

Electric current-induced magnetic fields (via electromagnetic induction) are divided into three groups according to their frequencies (Hz, 1/s). These frequency ranges are:

1. Extremely Low-Frequency Magnetic Fields (ELF-MF): These frequencies are in the range of 30-300 Hz. This group includes magnetic field frequencies of 50 - 60 Hz, especially generated at the electrical power distribution networks. Electrical cables and connectors are a major source of ELF-MF.

2. Intermediate Frequency Electromagnetic Fields (Range 300 Hz to 10 MHz): The magnetic fields in this group generally include the range of frequencies used in systems such as radio receivers and transmitters.

3. The high frequency or radio frequency region (10 MHz to 300 GHz). These are high-frequency carrier signals that are generally used in radio and television broadcasting to transmit information.

From the lower limits of intermediate frequency magnetic fields, frequencies above 300 Hz have thermal effects (1). While ELF-MF, which encloses magnetic fields below this frequency has no such thermal effect.

In particular, the effect of pulsed electromagnetic fields (PEMF), belonging to the ELF-MF group, has been studied in a variety of tissues and disease models and has been suggested as an adjuvant treatment in many studies (2-4).

Effect Mechanism of Magnetic Fields on Biological Systems

Magnetic field strength (H) (Amper/meter) that occurs during the transmission of the electric current generates magnetic flux density (B) (Tesla) in a material depending on the magnetic permeability (□) of the material (Henry/meter or Newton/Amper^2). The magnetic flux density, which can also be written as the response of the material to the applied magnetic field strength, can be written as the product of the magnetic field strength and the permeability of the material:

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$\boldsymbol{B} = \square \boldsymbol{H}$

In this regard, magnetic permeability is a measure of whether the material can generate a magnetic field within itself or how easily the material is affected by the applied magnetic field.

In free space (vacuum), the magnetic flux density in the matter will change proportionally to the universal constant $\square_0$:

$\mu_0 = 4\pi\ 10^{-7}\ (H/m, N/A^2)$

$\approx 1.257\ 10^{-6}\ (H/m, N/A^2)$

Since the absolute magnetic permeability of the material (μ_{matter}) has a different degree of permeability than the magnetic permeability of the vacuum, the relative magnetic permeability (μr) is used in the calculation of the magnetic permeability (a unitless permeability ratio of the material to the vacuum).

$\mu_r = \mu_{material} / \mu_0$ (The value of the relative magnetic permeability of vacuum is 1 according to this calculation.)

While magnetic permeability refers to a material's ability to generate a magnetic field within itself, magnetic susceptibility (χ) is the expression of the amount of magnetization when the material is left in the magnetic field:

$\chi = \mu_r - 1$

To examine the effects of electromagnetic fields on biological systems, the ability of the magnetic field to magnetize the material (formation of the dipole moment density) should be considered:

The magnetization of a substance is determined by the configurations (arrangement) of the electrons in the structure of its atoms. According to the Pauli exclusion principle, two electrons in an atom can never have the same set of quantum numbers (n, l, m_l, m_s) in terms of energy levels and position. The principal quantum number (n) describes the energy level of an electron (electron shell). The angular momentum quantum number (orbital quantum number) is defined as a subshell: It is the grouping of electrons in a shell according to the shape of the region of space they occupy. The magnetic quantum number (m_l) is used to describe possible orbitals within the subshell and their orientation in space. The spin quantum number (m_s) is a quantum number that describes the intrinsic angular momentum (or spin angular momentum or simply spin) of an electron or other particle. The magnetic quantum number, as the name suggests, determines the change in the energy level of the atom under the influence of an external magnetic field (Zeeman effect), and thus affects the energy of the electron only when the electron is in a magnetic field. The actual magnetic dipole moment of an electron on an atomic orbit results not only from the electron angular momentum but also from the spin of the electron, which is expressed by the spin quantum number. The magnetic moment, or magnetic dipole moment of the electron is the angular momentum of the electron with the electric charge, called spin, rotating about its axis as it moves in orbit.

The magnetic moment (m) measures the tendency of matter to align itself in a magnetic field and indicates the strength and direction of the material's magnetism.

How strongly a substance will be magnetized (M) is estimated utilizing the following formula;

$\mathbf{M} = m_{total}/V$

which is equal to the net magnetic moment (m_{total}) per unit volume (V).

The magnetic flux density is rewritten as;

$\boldsymbol{B} = \square_0(\boldsymbol{H}+\boldsymbol{M})$ ($\boldsymbol{H}$ and $\boldsymbol{M}$ have the same units—Ampere/meter.)

For materials that cannot be permanently magnetized, the magnetization strength is proportional to the applied magnetic field strength (H) and magnetic susceptibility χ:

$\boldsymbol{M} = \chi \boldsymbol{H}$

Magnetic susceptibility is a measure of how a material becomes magnetized in an applied magnetic field. Entities are classified as diamagnetism, paramagnetism, and ferromagnetism on the basis of their orientation to externally applied magnetic fields. The value of the χ determines to which of these classes the item belongs:

Diamagnetic materials: $-1 \leq \chi < 0$,
Paramagnetic materials: $0 < \chi < 0.01$
Ferromanyetik materials: $\chi >> 1$

Because diamagnetic materials have no net angular momentum and no unpaired electrons in the same orbital, their net spin is zero. Paramagnetic and ferromagnetic molecules are composed of atoms with permanent magnetic moments and non-zero net spins. Ferromagnetic materials are more sensitive/magnetized in an external magnetic field and retain their magnetic properties after the source of the magnetic field is removed. Paramagnetic substances, on the other hand, cannot retain their acquired magnetic properties after the source has been removed.

The magnetic susceptibility of a substance also defines the behavior of that substance in a magnetic field. The magnetic susceptibility of tissues in the human body varies within a range of $-10\text{-}5 < \chi < 10\text{-}5$. In this case, biological tissues lie in the diamagnetic or weakly paramagnetic range (5). This range of magnetic susceptibility is also compatible with studies showing that the fixed magnetic field has no significant effect on biological tissues (5-7). However, free radicals formed during many reactions in cells are paramagnetic because they contain unpaired electrons and have net magnetic moments in the magnetic field.

There are various studies examining the consequences of PEMFs on biological systems through physical and chemical mechanisms. These studies also indicate the effects of the magnetic field on radical pair formation (8).

Effect of ELF-MF on Free Radicals in The Cell

Free radicals are atoms or molecules that contain one or more unpaired electrons in their outermost orbit. They are formed by removing an electron from a non-radical atom or molecule or by adding an electron to a non-radical atom or molecule.

In general, free radicals are very reactive, as they tend to become energetically coupled. For the pairing state, they can interact with the atoms or molecules around them and make them reactive by gaining or losing electrons from them. An unstable molecule formed in this way can also cause various diseases by reacting with macromolecules such as lipids, DNA, and proteins that make up living things (9). Free radicals in the body mainly form hydroxyl (OH•), superoxide (O2•–), nitric oxide (NO•), nitrogen dioxide (NO2•), peroxyl (ROO•), and lipid peroxyl (LOO•) molecules (10). Molecules such as hydrogen peroxide (H2O2), ozone (O3), peroxynitrite (ONOO–), and lipid peroxide (LOOH), which are oxidizing agents although not free radicals, can also cause the formation of free radical reactions in living things (11). Among these molecules, commonly referred to as reactive oxygen species (ROS), radicals in particular are more reactive and therefore less stable than oxidants (12). ROS are continuously produced during cellular energy metabolism, activation of various signaling pathways and thus maintenance of the dynamic state of equilibrium in living organisms. For example, NO is an

intercellular messenger that modulates blood flow, thrombosis, and neuronal activity (13). The endothelial NO synthase (eNOS) enzyme is responsible for NO production in the vascular system and plays an active role in the fight against vascular diseases (14). In addition, immune system cells such as neutrophils, macrophages and monocytes secrete free radicals to destroy pathogenic microbes as a prerequisite for their defense mechanism (15). At a steady state, the production and destruction of free radicals and ROS in the cell are controlled by many different enzymes or chemicals (16).

In the literature, the effect of ELF-MF on free radical reactions were demonstrated (8, 17). In these studies, they examined the effects of ELF-MF on the nuclear spin levels and electron orbitals of free radicals. Accordingly, it has been shown that electromagnetic fields at certain frequencies cause alterations in the orbits of electrons and nuclear energy levels in the molecule. In addition, theoretical and experimental studies have shown that weak magnetic fields have significant effects on the stabilization half-lives of free radicals and radical pairing reactions (9, 18-20).

Effect of ELF-MF on Cellular Hemostasis

An ELF-MF application system generally features a power supply and Helmholtz coils (HCs) placed inside the Faraday cage, which is a metallic shield to prevent the ingress or egress of MF. The animals are placed inside to the Plexiglas cage and the cage is placed in the center of HCs.

In order to examine the MF-ROS interaction in experimental systems, the Helmholtz coil, which can generate a constant magnetic field, is widely used in laboratories. The Helmholtz coil consists of two symmetrical solenoid electromagnets on the same axes. Experimental groups placed in the center of the solenoids carrying an equal amount of electric current in the same direction are therefore exposed to the same amount of MF. The application protocols of the MFs, which consist of different intensities and frequencies, also differ in the studies. Scientists usually prefer to use the parameter sets in which they observed the effects of MF in their previous studies (21).

In experimental studies, it is known that changes in ROS levels can induce many antioxidant enzymes and non-enzymatic systems (26). Additionally, ELF-MF has been shown to increase the half-life of free radicals, particularly in cancer cells thus affecting cellular homeostasis (22).

The experimental studies show that, changes in ROS levels can induce many antioxidant enzymes and non-enzymatic systems in the cell (23-25). It was observed that ELF-MF caused an increase in the ROS species such as H_2O_2 in C2C12 skeletal muscle cell lines, and also an increase in catalase enzyme, the enzyme that breaks down H_2O_2 (26, 27). In a study performed on mouse macrophages, short-term (2 hours) MF applications caused changes in ROS levels and protein expressions that play a regulatory role in ROS activation, albeit temporarily (28). It has been shown in HL-60 leukemia cells that stress proteins, which are activated to protect the cell from oxidative stress (29), are induced together with ELF-MF application (30).

Along with studies showing an increase in ROS molecules, there are also studies showing decreases in ROS levels. In a study in which ELF-MF was applied to adult rats, oxidative stress was shown to decrease in the brain tissues of animals (31). It was also shown that the increased amount of ROS in rats with cardiac ischemia-reperfusion (I/R) injury decreased with the administration of ELF-MF and therefore the researchers proposed that the administration of ELF-MF may be an option to aid treatment (32).

There are also studies in the literature stating that the effect of ELF-MF on ROS molecules or on proteins that activate various pathways in which ROS will be activated may depend on the frequency and/or application time. When the effect of ELF-MF on oxidative stress in rat heart homogenates was examined in terms of hydrogen peroxide (H_2O_2), total free sulfhydryl groups, and reduced glutathione concentrations, it was found that the increase in ROS and plasma antioxidant capacity became statistically significant with exposure time (33). The effect of MF on ROS formation was also evaluated in another study as a function of exposure times in rat brain tissue: ELF-MF application for 30 minutes per day for 10 days caused lipid peroxidation as a result of increased ROS, but researchers assessed that application of the same frequency for 60 minutes per day for the same period increased the total protein and free sulfhydryl groups as that activation of adaptation mechanisms (34). In a study investigating the effect of long-term application of ELF-MF on the antioxidant enzyme capacities of young and elderly patients, it was shown that MF, although different in the two groups, altered the expression level and activities of macromolecules such as superoxide dismutase, glutathione peroxidase, catalase, glutathione reductase, which are the main antioxidant enzymes (23). In the studies we conducted on the vascular smooth muscle in our own laboratory, the effects of ELF-MF application were demonstrated through NO and H_2O_2 (35, 36). We observed that MF administration to rats (40 Hz, 1.5 mT for 1 hour per day for 30 days) increased eNOS (endothelial nitric oxide synthase) expression in rat aortas compared to untreated tissues. We concluded that such an effect of MF on healthy tissues may shift cellular mechanisms into a new steady state, which may be manifested by altered cellular or functional responses to homeostatic dysfunction.

Along with all these studies, there are also publications that did not detect a change in oxidative stress after ELF-MF applications (37, 38). However, it is generally emphasized that this may be a result of differences depending on the cell types to which MF is applied and the variety of applied MF frequency, severity, and duration.

Results

The role of MF in cellular homeostasis, which can affect both the amount of ROS continuously produced in cells and the activation of proteins responsible for their production, remains an issue that requires detailed studies.

This is important in two respects:

1. In a healthy cell, the effect of ELF-MF on ROS can bring cellular systems to a new stable state, which in turn can change the response of the cell in case of disease.

2. An adapted state can lead to confusion when interpreting the effect of ELF-MF in the disease state. For example, a positive effect such as increasing the apoptosis pathways of ELF-MF in cancer cells (or cell lines derived from cancer cells) will change the meaning of the study if the cell is disregarded as a cancer cell and interpreted as ELF-MF triggers apoptosis in cells (39).

Therefore, before assessing the relatively positive or negative effects of MF in disease or various health problems, it is essential to better comprehend its impacts on cellular homeostasis.

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Targeted Genome Editing Technologies: Paradigm Shift in Modern Medicine

Gizem Inal

1. The Landscape of Genomic Mutations and the Birth of Gene Therapy

Genomic mutations, characterized by permanent alterations in the DNA sequence, occur via various mechanisms such as substituting a base pair or adding or removing one or more base pairs. The impact of these mutations depends largely on their location within the DNA structure. Silent mutations in nonessential parts of DNA typically have negligible effects on gene function. However, non-silent mutations often have detrimental consequences, with a few exceptions that confer biological advantages (Wang & Qi, 2016).

Genetic disorders primarily stem from these mutations, particularly those located in a single gene. Disorders such as sickle cell disease and Duchenne muscular dystrophy, affecting millions of individuals globally, are linked to monogenic mutations. Given the profound impact of these mutations, therapeutic approaches targeting these genes are promising for treating genetic disorders.

Gene therapy began in the 1960s with the discovery of fundamental concepts of gene transfer and the subsequent development of transfection techniques. The 1970s saw the discovery of ligation and restriction enzymes, which formed the basis of gene manipulation. The advent of recombinant DNA technology has facilitated the insertion of selected therapeutic genes into vectors, enabling the use of viral vectors as efficient tools for gene transfer (Naldini, 2015).

The conventional gene therapy approach involves substituting defective genes or gene products with wild-type genes using viral vectors. While initial attempts using ex vivo retrovirally modified cells were successful, they also led to serious adverse events, including patient death (Hacein-Bey-Abina et al., 2003). Approximately 20 conventional gene therapy products have been approved by the US Food and Drug Administration (FDA) as of now (Dunbar et al., 2018). Despite these advances, conventional gene therapy is associated with potential risks, such as serious immune reactions, potential risk of oncogenesis, and insufficient awareness of long-term adverse side effects (Cavazzana et al., 2021). Targeting the mutated part of a gene directly and specifically can mitigate the risk of oncogenesis associated with conventional gene therapy, resulting in lower side-effect rates and more accurate treatment.

2. Evolution of Genome Editing Technologies: From ZFNs to CRISPR/Cas9

Targeted DNA modifications primarily rely on the formation of double-strand breaks (DSBs) through endonuclease activity and resolution of these breaks through cellular DNA repair mechanisms (Jasin & Haber, 2016). Gene editing technology has evolved through three major generations, starting with first-generation zinc-finger nucleases (ZFNs), moving to second-generation transcription activator-like effector nucleases (TALENs), culminating in the third and most commonly used technology, Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) (Doudna & Charpentier, 2014). Unlike

ZFNs and TALENs, CRISPR technology improves gene-editing efficiency by directing Cas proteins to specific locations in the genome (Jinek et al., 2014).

ZFNs, the first genome editing technique, comprise zinc finger proteins and the non-specific catalytic domain of the FokI endonuclease. Subsequently, a Transcription Activator-like Effector (TAL) conjugated with FokI, also known as TALEN, was developed, which marked a significant advance in the research field. The discovery of the CRISPR system heralded the improvement of the most widely used genome-editing method, CRISPR/Cas-mediated genome editing. CRISPR/Cas provides efficient editing capabilities and theoretically carries a lower risk of off-target effects than ZFNs, particularly TALENs. Owing to its ease of design and use, CRISPR/Cas-mediated genome editing is quickly integrated into everyday laboratory work (Cong et al., 2013).

3. CRISPR/Cas9 Technology: Revolutionizing the Field of Genome Editing

CRISPR/Cas technology has emerged as a potent gene-editing tool that enables researchers to precisely alter the DNA structure. Discovered initially as an adaptive bacterial immune system providing defense against viral infections, researchers soon realized that the CRISPR/Cas system could be repurposed for targeted gene editing across a variety of organisms (Barrangou et al., 2007).

The CRISPR/Cas system primarily comprises two main components: guide RNA (gRNA) and the Cas protein. A specially designed RNA molecule containing a sequence complementary to the target DNA is called guide RNA (gRNA). The Cas protein is an enzyme acting as molecular scissors, capable of cleaving DNA at specific locations. This gene-editing system exploits a defense mechanism where bacteria and archaea acquire small DNA segments from invading viruses or other foreign DNA and incorporate them into their own genome. These DNA segments, known as CRISPR arrays, are transcribed into a long RNA molecule, the precursor CRISPR RNA (pre-crRNA), which the Cas protein processes to produce shorter RNA segments called CRISPR RNA (crRNA). The crRNA binds to a separate RNA molecule called trans-activating CRISPR RNA (tracrRNA) to form a complex. For simplicity, these two RNA molecules are sometimes engineered into a single chimeric RNA molecule, the single-guide RNA (sgRNA). The crRNA-tracrRNA (or sgRNA) complex binds to the Cas protein to form an active complex. This complex is guided by the crRNA sequence to the target DNA sequence that matches its complementary sequence. The PAM (protospacer-adjacent motif) sequence, a short sequence of nucleotides adjacent to the target DNA sequence, is essential for the specificity of the CRISPR-Cas system, distinguishing between foreign DNA, such as viral DNA, and the host organism's own DNA. When using the CRISPR-Cas system for gene editing, the Cas protein must recognize and bind to the target DNA sequence, which is only possible if a specific PAM sequence follows it. This requirement prevents the Cas protein from mistakenly binding to the host organism's own DNA, thus avoiding unintended modifications (Mali et al., 2013).

Repair Pathways and Implications for Therapeutic Genome Editing

Once the CRISPR/Cas complex reaches the target DNA, the Cas protein introduces a double-strand break (DSB) at a specific location guided by the crRNA. The cell's inherent DNA repair mechanisms are stimulated, leading to one of two primary repair pathways: Non-Homologous End Joining (NHEJ) and Homology-Directed Repair (HDR) (Jinek et al., 2012).

3.1 Non-Homologous End Joining (NHEJ) and Homology-Directed Repair (HDR)

NHEJ, an error-prone process, ligates the DNA break ends directly without requiring a homologous template. This repair often results in small insertions or deletions (indels) at the DSB site, which can disrupt the gene's function if within a gene coding region (Lieber, 2008).

HDR, on the other hand, requires a donor DNA template and allows for precise DNA sequence changes during the repair process. Scientists can introduce specific genetic modifications at the target site by supplying a DNA template with the CRISPR/Cas components (Chu et al., 2015).

4. Therapeutic Genome Editing: Applications, Limitations and Future Outlook

CRISPR/Cas9 has substantially impacted various medical fields, notably oncology, infectious diseases, and monogenic disorders.

4.1 Oncology and CRISPR/Cas9

CRISPR/Cas9 is promising in cancer research, although its application in human cancer treatment requires further exploration. Scientists use CRISPR/Cas9 to generate accurate cancer models in the laboratory by introducing specific genetic mutations associated with cancer development into cells or animal models. This approach enables the study of molecular mechanisms of cancer and testing of potential therapies more effectively (Sanchez-Rivera & Jacks, 2015).

Researchers can identify cancer-related genes and study their roles in development and progression by conducting wide-ranging genetic screens. The systematic editing of genes in cancer cells can uncover effects on cell growth, metastasis, drug resistance, and other crucial cancer-related processes (Munoz et al., 2016).

CRISPR/Cas9 also holds promise for revolutionizing gene therapy by enabling precise modifications of the human genome. Researchers are exploring the use of CRISPR/Cas9 to develop personalized therapies that can selectively kill cancer cells or make them more vulnerable to existing treatments (Weber et al., 2020).

CRISPR-based diagnostic platforms, which detect cancer-related mutations and markers in patient samples, are under development. These innovative diagnostic tools could improve patient outcomes by enabling early detection and intervention (Tang et al., 2017).

However, significant technical and ethical challenges must be addressed before widespread use in human cancer treatment. The technology must be further refined to ensure safety, accuracy, and efficiency. Extensive preclinical and clinical trials will be required to evaluate the long-term effects and potential side effects of CRISPR-based therapies. Regulatory and ethical considerations surrounding gene editing must also be addressed to ensure responsible and equitable use of this technology.

4.2 Infectious Diseases: HIV and CRISPR/Cas9

CRISPR/Cas9 technology has been used to understand the genes involved in HIV infection. By selectively disabling specific genes, researchers can observe how genetic changes affect the cell's resistance or susceptibility to HIV. CRISPR/Cas9 can help identify potential targets for antiviral drugs (Kaminski et al., 2016).

Moreover, researchers are exploring CRISPR/Cas9 as a potential gene therapy approach for HIV. The aim is to modify the genetic material of HIV-infected cells to make them resistant to the virus. However, transitioning this approach into a safe and effective therapy requires

further research and refinement. One significant challenge in curing HIV is the existence of latent viral reservoirs; cells in which the virus persists in a dormant state. CRISPR/Cas9 has been investigated as a tool to target and eliminate these reservoirs, potentially offering a functional cure for HIV (Kaminski et al., 2016).

4.3 Monogenic Disorders and CRISPR/Cas9

Monogenic disorders, diseases caused by mutations in a single gene, could potentially be treated using CRISPR/Cas9 by directly correcting the disease-causing mutation in the patient's DNA. This approach has shown promise in preclinical studies for several monogenic disorders, including sickle cell anemia, transfusion-dependent thalassemia, cystic fibrosis, and Duchenne muscular dystrophy (Ma et al., 2021).

CRISPR/Cas9 can also regulate specific genes and gene expression, especially when the disease-causing mutation cannot be easily corrected or other genetic factors contribute to the disorder. Despite its potential, several challenges must be addressed before its widespread use in the treatment of monogenic disorders, including efficient delivery of CRISPR components to target cells, off-target effects, and potential immune responses to CRISPR components.

5. Rewriting Life: CRISPR-Cas9 mediated Immortalization

Prevention of genetically induced replicative senescence called immortalization is a promising approach for bio-artificial organs aimed at obtaining cellular materials for cell therapy or overcoming the shortage of donor materials.

Senescence is a biological process characterized by a state of irreversible growth arrest and functional decline in cells or organisms. It is a natural part of the aging process and can also be induced prematurely by various cellular stresses. Senescence can occur in individual cells or at the level of entire tissues or organisms (Regulski, 2017).

Senescence plays a role in various physiological and pathological processes. It acts as a protective mechanism by preventing damaged or potentially cancerous cells from proliferating. However, the accumulation of senescent cells over time can contribute to aging and age-related diseases. Senescent cells can exhibit altered metabolism, impaired tissue repair, and promote chronic inflammation, all of which can negatively impact tissue and organismal function. Cellular senescence is triggered by a variety of factors, including DNA damage, telomere shortening, oxidative stress, oncogene activation, and inflammation. These factors can lead to the activation of specific signaling pathways that ultimately result in the induction of senescence (Shmulevich & Krizhanovsky, 2021).

CRISPR technology can be employed to facilitate the immortalization of cells by targeting and modifying specific genes involved in the regulation of cell division and senescence. Researchers can use CRISPR to disrupt or modify genes responsible for controlling telomere length, DNA repair mechanisms, or cell cycle checkpoints. By manipulating these genes, researchers can potentially induce immortalization in specific cell types. For example, the tumor suppressor genes TP53 (p53) and RB1 (retinoblastoma 1) play crucial roles in cell cycle control and senescence. Inactivation or modification of these genes can lead to the immortalization of cells. By using CRISPR-Cas9, researchers can introduce specific mutations, deletions, or insertions in the target genes, effectively altering their function or disrupting their activity. These modifications can bypass the natural mechanisms that limit the replicative lifespan of cells and enable continuous cell division (Salama et al., 2014).

CRISPR/Cas technology allows for precise modifications of the genome, including the correction of genetic mutations associated with cellular senescence. CRISPR/Cas can be used

to correct genetic mutations that contribute to replicative senescence. This approach has shown promise in preclinical studies for correcting genetic defects associated with premature aging syndromes, which are often characterized by accelerated cellular senescence (Peng et al., 2023).

5.1 Targeting Telomeres and Telomerase

Telomeres are repeating nucleotide hexamers of DNA that are found at the ends of chromosomes. They play a crucial role in preserving the stability and integrity of the genome. Telomeres consist of repetitive nucleotide sequences, such as TTAGGG in humans, which are typically repeated thousands of times. One of the primary functions of telomeres is to protect the genetic information encoded in chromosomes during cell division. During DNA replication, the conventional replication machinery is unable to fully duplicate the ends of linear chromosomes. As a result, telomeres act as protective caps, preventing the loss of important genetic material from the ends of chromosomes (Turner et al., 2019).

Telomeres also play a role in the aging process and cellular lifespan. With each cell division, the telomeres become slightly shorter (Harley, 1992). Eventually, when telomeres become critically short, cells may enter a state of senescence or undergo programmed cell death (apoptosis). This progressive telomere shortening is associated with aging and age-related diseases. Telomere shortening is a hallmark of replicative senescence (Shay & Wright, 2005). The CRISPR/Cas system can potentially be used to extend telomeres by introducing telomere repeat sequences to compensate for the natural attrition. However, this approach is complex due to the challenges associated with the delivery and regulation of the telomerase enzyme, which is responsible for elongating telomeres. Further research is required to develop safe and efficient methods for telomere extension using CRISPR-Cas9 (Porika et al., 2022).

Telomerase is an enzyme that is involved in the maintenance and elongation of telomeres. Telomeres are repetitive DNA sequences located at the ends of chromosomes that protect the genetic information from degradation and fusion with other chromosomes. They act as a kind of "buffer" region that prevents the loss of essential genetic material during DNA replication. Telomerase is a unique enzyme because it has the ability to add telomeric DNA repeats onto the ends of chromosomes. This counteracts the natural shortening of telomeres that occurs with each round of cell division. The enzyme achieves this by using an RNA molecule as a template to synthesize new DNA sequences that match the telomeric repeats (He & Feigon, 2022).

The core components of telomerase are the telomerase reverse transcriptase (TERT) protein and the telomerase RNA component (TERC). TERT serves as the catalytic subunit responsible for the enzymatic activity, while TERC provides the template for the addition of telomeric DNA (Wang et al., 2019).

In cells with active telomerase, the enzyme extends the telomeres, maintaining their length and stability. This is particularly important in cells that undergo frequent divisions, such as germ cells (sperm and egg cells) and certain types of stem cells. However, in most somatic cells (non-reproductive cells), telomerase activity is low or absent, resulting in gradual telomere shortening with each replication. This shortening is associated with cellular aging, senescence, and an increased risk of genomic instability. The regulation of telomerase activity is tightly controlled, with various factors influencing its expression and activity levels. Mutations or dysregulation of telomerase can have significant implications for aging, disease, and cellular function (Giardini et al., 2014).

Targeting telomere and telomerase using CRISPR-based approaches has been a topic of interest in the field of aging and disease research. While the potential use of CRISPR to modify telomerase for therapeutic purposes is still in the early stages of development, several strategies have been proposed and explored in preclinical studies (Beishline et al., 2017).

CRISPR can be used to regulate the expression of telomerase by targeting the promoter region of the TERT gene, which encodes the catalytic subunit of telomerase. By modifying the promoter, researchers can potentially increase or decrease telomerase activity in specific cell types. This approach has been investigated to address both aging-related conditions and cancer, where modulating telomerase expression can have different therapeutic implications (Chiba et al., 2017).

CRISPR can be used to modify the telomerase genes themselves. For example, by introducing specific mutations in the TERT or TERC genes, researchers can investigate the functional consequences and potential therapeutic applications of these modifications. This approach can help elucidate the role of specific telomerase variants in aging and disease processes (Xi et al., 2015).

It's important to note that the application of CRISPR in targeting telomerase for therapeutic purposes is still largely in the preclinical stage. Many challenges and considerations need to be addressed before any potential clinical applications can be realized. These include issues related to delivery methods, off-target effects, ethical considerations, and the complex regulation of telomerase in different cell types (Park & Beal, 2019). Further research is needed to evaluate the safety and efficacy of CRISPR-based approaches for telomerase targeting, as well as to determine the potential benefits and limitations in various aging-related conditions and diseases. It is an active area of investigation, and future advancements in CRISPR technology may provide valuable insights into the therapeutic potential of targeting telomerase (Gao et al., 2022).

5.2 Immortogene Insertion

CRISPR/Cas9-mediated immortogene insertion is a technique that holds great potential for gene editing due to its ability to precisely target specific regions of the genome. This technique offers several advantages over traditional methods such as lentivirus transduction. One of the key benefits of CRISPR/Cas9-mediated immortogene insertion is its gentle genome editing capability. The CRISPR/Cas9 system induces a double-strand break. This break can be repaired by the cell's natural DNA repair machinery, allowing for the precise insertion of the desired immortogene at the target site. Compared to other techniques, such as random integration by lentivirus transduction, CRISPR/Cas9-mediated editing allows for more controlled and predictable modifications to the genome (Sutyagina et al., 2023).

Furthermore, the use of CRISPR/Cas9 enables gene insertion into "safe harbors." Genetic safe harbors (GSHs) are specific genomic regions that are well characterized and have been shown to tolerate genetic modifications without disrupting normal cellular functions. By inserting immortogenes into safe harbors, researchers can minimize the risk of unintended consequences or deleterious effects on the cell's physiology. This approach increases the likelihood of stable and predictable gene expression over time (Papapetrou & Schambach, 2016).

Another advantage of CRISPR/Cas9-mediated immortogene insertion is the reduced severity of "footprint" mutations. Footprint mutations refer to unintended alterations in the genome that may occur during the gene editing process. Compared to lentivirus transduction, which often involves random integration of foreign DNA, CRISPR/Cas9-mediated editing offers greater precision and reduces the likelihood of off-target effects or disruptive mutations (Pich et al., 2019).

Given these advantages, it is reasonable to consider CRISPR/Cas9-mediated immortogene insertion as a favorable alternative to lentivirus transduction. However, it's important to note that while CRISPR/Cas9 technology has revolutionized gene editing, there

are still challenges to overcome. Off-target effects, incomplete editing, and efficient delivery of the CRISPR components to the target cells remain areas of active research and optimization. CRISPR/Cas9-mediated immortogene insertion may still be primarily presented in single studies and ongoing research (Hu et al., 2017). The field of CRISPR/Cas9-mediated gene editing is rapidly evolving, and new advancements and techniques may have emerged since then. It is always advisable to consult the most up-to-date scientific literature and consult with experts in the field for the latest information on specific applications of CRISPR/Cas9 technology.

However, it is important to note that cell immortalization is a complex process, and solely using CRISPR may not be sufficient to achieve indefinite cell division. Various factors, including the activation of telomerase, alterations in cell signaling pathways, and the expression of oncogenes, play critical roles in cell immortalization. CRISPR can be a valuable tool in the overall process, but additional steps and factors are often required for successful cell immortalization.

6. Conclusions

While genome editing techniques are advancing rapidly, the application of these techniques in humans raises serious ethical concerns. Editing efficiency is still low, and predicting potential side effects is challenging. Clinical trials, which are essential for shaping future perspectives, require time; as such, there is limited available reliable information.

CRISPR/Cas9 technology has revolutionized the field of genetic engineering due to its simplicity, efficiency, and versatility. It has enabled researchers to study gene functions, develop disease models, and explore potential therapeutic applications. However, the technology is still rapidly evolving, and ethical considerations and safety precautions must be addressed when using CRISPR/Cas9 in human applications.

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Exploring the Therapeutic Potential and Practical Considerations of Retinoids in Dermatological Practice

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The Role of Retinoids in Dermatology and Brief History

Retinoids, as structural and functional analogs of vitamin A, exhibit a diverse array of effects on cellular differentiation, proliferation, the immune system, and embryonic development. Owing to these versatile properties, a spectrum of vitamin A derivatives have secured approval for treating a range of dermatological conditions including, but not limited to, acne, photoaging, and psoriasis. This article delves into the categorization of retinoids and their respective applications within dermatology, offering a comprehensive overview of their therapeutic potential.

Retinoic acid (RA), also known as all-trans retinoic acid (ATRA), constitutes a biologically active form of vitamin A, embodying a significant biochemical element in the spectrum of retinoids (del Mar Vivanco-Ruiz, Tiollais, Stunnenberg, & Dejean, 1990). Serving as a key metabolite of vitamin A, RA exacts a consequential influence on cellular function via selective intracellular isomerization to all-trans-retinoic acid and through binding to specific retinoic acid receptors (RARs)(Tsukada et al., 2000). The retinoic acid receptors, as integral nuclear receptors, perform the role of gene expression regulators, connecting with the cis-acting retinoic acid-responsive elements within the target genes, which subsequently steers pivotal physiological processes such as immune response, growth and development, reproduction, and the visual system (de Thé, Vivanco-Ruiz, Tiollais, Stunnenberg, & Dejean, 1990).

Retinoids, synthesized endogenously, trace their origins back to vitamin A. The formation of RA, in particular, encompasses a feedback loop that controls retinol esterification (Kurlandsky, Duell, Kang, Voorhees, & Fisher, 1996). The genesis of all-trans retinoic acid is not limited to endogenous production but extends to exogenous sources, primarily including animal-derived products like liver, kidney, egg yolks, and butter. In addition to these, dietary supplements also serve as a significant external provider of RA (Kurlandsky et al., 1996).

In the context of human skin, RA controls its own biosynthesis from all-trans retinol, hinting at the intricate mechanism underlying retinoid metabolism and function (Iwata et al., 2004). Retinol, retinal, retinoic acid, and retinyl esters, being primarily sourced from animal-based food products, also underline the important dietary contribution to retinoid metabolism (Sm it, de Jong, de Jongh, & van de Kerkhof, 2000).

Retinoids, the class of compounds derived from Vitamin A, have held a crucial role in dermatology since the early 20th century. Wolbach initially delineated their significance in cutaneous biology, observing that vitamin A deficiency induced defective keratinization in conditions such as epidermal hyperkeratosis and squamous metaplasia of mucous membranes (Wolbach & Howe, 1925). These anti-keratinizing properties laid the groundwork for the application of retinoids, both systemically and topically, in treating disorders of keratinization (Sorg, Kuenzli, & Saurat, 2007).

Early clinical explorations with oral vitamin A revealed a precarious balance between efficacy and toxicity, catalyzing endeavors to design synthetic retinoids that would exhibit enhanced therapeutic potency and reduced toxicity. The first dermatological application was reported in 1943 by Straumford, who used retinoids to treat acne vulgaris (Eichenfield, Sprague, & Eichenfield, 2021). In 1962, Stuttgen broadened their use by introducing topical tretinoin for keratinization disorders, and in 1969, Kligman et al. showcased the efficacy of topical tretinoin in treating acne vulgaris (Eichenfield et al., 2021).

The use of retinoids was significantly advanced in 1982 when the FDA approved isotretinoin for nodulocystic acne treatment. Soon after, Bollag (1972) introduced the use of etretinate and acitretin in dermatology, which were eventually used to treat psoriasis in 1986. By 1988, acitretin had largely replaced etretinate (Orfanos, Zouboulis, Almond-Roesler, & Geilen, 1997).

With the new millennium came the introduction of bexarotene for treating cutaneous T-cell lymphoma (CTCL) and all-trans retinoic acid (allitretinoin) for Kaposi's sarcoma treatment, both in 1999 (Engels et al., 2003). These developments were, however, delayed due to concerns about increased teratogenicity following the thalidomide tragedy. Yet, the late 1970s saw Peck et al. demonstrating the effectiveness of oral isotretinoin in treating lamellar ichthyosis and other keratinization disorders, and in 1999, the FDA approved the topical use of alitretinoin for treating cutaneous Kaposi's sarcoma. Alitretinoin has also been authorized for severe and persistent hand eczema treatment in certain regions outside the United States (Nettis et al., 2020).

Pharmacology of Retinoids

Our understanding of the molecular pharmacological properties and retinoid action mechanisms has been significantly advanced with the discovery of nuclear receptors, specifically the retinoic acid receptors (RARs) and retinoid X receptors (RXRs). This led to the development of third-generation retinoids, including topical adapalene (for acne), topical tazarotene (for psoriasis and acne), and oral and topical bexarotene (for CTCL) (Sato, Fujimura, Kambayashi, Hashimoto, & Aiba, 2018; Ziouzenkova & Plutzky, 2008).

Retinoids, biologically active derivatives of Vitamin A, orchestrate a multitude of biological processes, including cellular growth, differentiation, morphogenesis, and immunomodulation, while also inhibiting tumor progression. The intricate biological functioning of retinoids extends to their metabolism within the body. Predominantly, retinyl esters are found within the lumen of the intestine, where they are absorbed and hydrolyzed into retinol, the chief dietary derivative of vitamin A (Ziouzenkova & Plutzky, 2008).

The ensuing transportation of retinol from the liver, its principal storage site, to various target cells is a coordinated process. This transfer is mediated via a complex consisting of retinol-binding protein (RBP) and transthyretin (Berry, Jin, Majumdar, & Noy, 2011). The facilitation of this transfer is carried out by STRA6, a dimeric transmembrane protein that functions as an RBP-retinol receptor. Once the retinol is absorbed by the target cells, it undergoes oxidation to retinaldehyde, followed by an irreversible conversion to retinoic acid (Berry et al., 2011). The retinoic acid, thus produced, serves as a signaling molecule that can bind to nuclear receptors to regulate gene expression, substantiating the significant role retinoids play in human physiology and pathology (Muenzner et al., 2013).

Retinoids, as potent regulators of cellular growth, differentiation, and apoptosis, have garnered significant interest in both dermatological and cancer therapeutics. These compounds, which are derivatives of Vitamin A (retinol), can be divided into three generations based on their chemical structures, providing a spectrum of selectivity and potency profiles in their interactions with retinoid receptors.

Classification of Retinoids

The first-generation retinoids, characterized as non-aromatic, include compounds such as tretinoin (all-trans retinoic acid), isotretinoin (13-cis retinoic acid), alitretinoin (9-cis retinoic acid), all-trans retinoyl β-glucuronide, and fenretinide. These compounds are synthesized via chemical modifications of the polar end group and polyene side chain of vitamin A, offering a foundational structure-function relationship in retinoid biology (Mukherjee et al., 2006).

Second-generation retinoids, referred to as monoaromatic retinoids, are more complex, with their modifications centered around the cyclic portion of vitamin A. This class includes etretinate, acitretin, and motretinide. These alterations allow for a more selective receptor interaction compared to their first-generation counterparts (Mukherjee et al., 2006).

Third-generation retinoids, also known as arotinoids, are categorized as polycyclic due to their complex structure. This group, which includes adapalene, bexarotene, tazarotene, tretinoin, and arotinoid sulfones, exhibits greater receptor specificity due to the cyclization of the polyene side chain. Adapalene, a naphthoic acid derivative, presents a unique case as its structure and activity do not precisely fit into any of the established generations (Mukherjee et al., 2006). While the above three generations provide a comprehensive spectrum of retinoid compounds, recent developments have also led to the synthesis of newer retinoids, including Seletinoid G, Aratinoid, and Etretin. Some authors refer to these as the potential fourth generation of retinoids, reflecting the continuing evolution and expansion of retinoid chemistry (Mukherjee et al., 2006). It's worth noting that due to their lipophilic properties, retinoids demonstrate significantly increased oral bioavailability when administered with food, especially a fatty meal. Further, retinoid metabolism primarily occurs in the liver (Orfanos et al., 1997).

Exploring Specific Retinoids

Tretinoin

The pharmacokinetics of retinoids are considerably impacted by their lipophilic nature. When administered orally, their bioavailability is substantially improved if ingested with food, particularly meals high in fat content. Retinoids are primarily metabolized in the liver, underscoring the significance of hepatic function in the therapeutic use of these compounds (Shirakami, Lee, Clugston, & Blaner, 2012). Since its approval by FDA in 1971 as a treatment for acne vulgaris till now tretinoin has been proven to be an effective first-generation retinoid used widely within clinical dermatology (Thielitz, Abdel-Naser, Fluhr, Zouboulis, & Gollnick, 2008). In 1995, the therapeutic applications of tretinoin expanded with its use in the treatment of photoaging.

In the treatment of acne vulgaris, tretinoin demonstrates efficacy through the reduction of microcomedone formation, the regulation of follicular keratinization, and the promotion of keratinocyte autolysis. It is commercially available in multiple formats, including creams, gels,

and solutions, with concentrations ranging from 0.01% to 0.1% (Dunlap, Mills, Tuley, Baker, & Plott, 1998).

In photoaged skin, tretinoin exerts a multitude of beneficial effects. It increases the thickness of the basal and granular layers, diminishes melanocyte activation and melanin distribution, and augments the secretion of glycosaminoglycans into the intercellular space (Mukherjee et al., 2006). Moreover, it stimulates the synthesis of collagen and elastin, which, coupled with its other effects, results in noticeable improvement in skin smoothness and firmness within 2-4 weeks, reduction of fine lines and hyperpigmentation within 2-4 months, and potentially a significant decrease in deep wrinkles after approximately six months of use (Mukherjee et al., 2006).

Oral tretinoin, while not providing substantial advantages over vitamin A, finds utility in promoting cellular differentiation and is specifically effective in managing acute promyelocytic leukemia. Topically applied tretinoin, on the other hand, boasts numerous therapeutic benefits, including the regulation of follicular keratinization, reduction of inflammation through TLR-2 and Interleukin-6 inhibition, comedolytic action, tyrosinase inhibition, melanosome transfer prevention, regulation of keratinocyte proliferation and differentiation, reduction of epidermal atypia and dysplasia, and stimulation of new collagen production (Ascenso et al., 2014).

Clinical application of tretinoin warrants several key considerations such as nighttime application, sun protection due to increased UV sensitivity, treatment application to the entire face when used for acne, and potential for initial irritation with subsequent development of tolerance. Short contact therapy, involving tretinoin application for 30-60 minutes followed by washing, may be implemented to minimize irritation. Furthermore, due to its pregnancy category C status, tretinoin use during pregnancy should only occur under the guidance of a healthcare professional due to potential fetal risks (Ascenso et al., 2014).

Isotretinoin

Isotretinoin, also recognized by its chemical name 13-cis retinoic acid, is a naturally occurring retinoid derivative of vitamin A metabolism. It stands out as the inaugural retinoid utilized for systemic treatment and traces its therapeutic history back to the 1970s, where it was initially employed in the management of ichthyotic disorders. It is notably effective in addressing nodulocystic acne and represents the 13-cis isomer of tretinoin (Fallah & Rademaker, 2021). The United States Food and Drug Administration (FDA) has sanctioned isotretinoin for oral administration exclusively. It is classified under pregnancy category X, which signifies a contraindication during pregnancy due to established risks (Ibrahim et al., 2021).

Isotretinoin exerts its therapeutic influence through its affinity for retinoic acid receptors (RARs). Its primary indication is acne, although it has demonstrated efficacy in several other dermatological conditions typically responsive to topical retinoids. These encompass nodulocystic acne, inflammatory acne with accompanying scarring, acne provoking significant psychological distress, pyoderma faciale, severe rosacea, hidradenitis suppurativa, dissecting cellulitis, Darier's disease, pityriasis rubra pilaris, and lichen planus characterized by widespread, hypertrophic, or erosive involvement (Younis & Al-Harbi, 2019).

Physiological concentrations of isotretinoin and its main metabolites, t-RA and 4-oxo-isotretinoin, are attainable within two weeks following its discontinuation. This timeline infers

an adequate safety margin of one month of contraceptive use to circumvent teratogenicity (Ibrahim et al., 2021)

Recommended standard dosages for isotretinoin administration are as follows:

1. An initial regimen of 1 mg/kg/day for a period of 4-5 months.

2. Start with a dosage of 0.5 mg/kg/day, subsequently increasing the dosage over time.

3. A total cumulative dosage ranging between 120-150 mg/kg.

4. For fulminant acne, a combination with 0.5-1 mg/kg/day of prednisolone is recommended.

5. For hidradenitis suppurativa, a higher dosage of 1-2 mg/kg/day is advised.

6. In the case of lichen planus exhibiting widespread, hypertrophic, or oral-erosive characteristics, concurrent use of low-dose steroids is recommended (Themes, 2019).

Alitretionin

Alitretinoin, chemically known as 9-cis-retinoic acid, is a first-generation retinoid with a unique capability to bind all retinoid receptors. It exhibits a variable half-life between 2 to 10 hours, and its clearance predominantly occurs via renal excretion. Upon cessation of treatment, alitretinoin concentrations are observed to normalize within a period of 1-3 days (Diepgen, Pfarr, & Zimmermann, 2012). This retinoid manifests both immunomodulatory and anti-inflammatory characteristics. Its ability to bind to both retinoid X receptors (RXRs) and retinoic acid receptors (RARs) underscores its versatility, positioning it as an endogenous retinoid consistently present in circulation (Diepgen et al., 2012). FDA approved the use of alitretinoin to manage Kaposi's sarcoma in 1999, and it can exert anti-proliferative effects via RAR mediation due to its dual ability of binding with both RXR and RAR receptors as well as trigger apoptosis through its association with RXR. The potential efficacy of alitretinoin may extend beyond its use in treating Kaposi's sarcoma to include the management of skin aging and pyogenic granuloma.

In the specific context of Kaposi's sarcoma, alitretinoin mitigates the proliferation of skin lesions by reducing the presence of growth factors and interleukin-6 in the sarcoma cells (Alsenaid, Alamri, Ruzicka, & Wolf, 2020). Oral administration of alitretinoin has found a niche in the treatment of severe chronic hand eczema unresponsive to potent topical steroids. However, the exact mechanistic pathway underlying its efficacy in this indication remains undetermined.

Asitretin

Asitretin, despite its widely observed clinical efficacy, still presents an enigmatic mechanism of action. Its therapeutic impact is more pronounced at higher dosages (50-75 mg) relative to lower dosages (10-25 mg). An initial therapeutic response is generally observed within 4-6 hours, with full effect requiring approximately 3-4 months. Asitretin demonstrates rapid onset and necessitates prolonged treatment duration. Notably, it exhibits an optimal response in lamellar ichthyosis, and in conditions like bullous ichthyosiform erythroderma and Darier's disease, maintenance therapy with low-dose retinoid treatment (<1 mg/kg/day) is advocated to prevent exacerbations (Digiovanna, Mauro, Milstone, Schmuth, & Toro, 2013; Orfanos et al., 1997).

Two oral retinoids, asitretin and etretinate, present notable differences: *Lipophilicity*: Asitretin is considerably less lipophilic than etretinate, with etretinate displaying around 50 times more lipophilicity. *Elimination half-life*: The elimination half-life of asitretin spans 2-4 days, a stark contrast to etretinate's lengthy elimination half-life of 120 days or more. *Elimination rate*: Over 98% of asitretin is eliminated from the body within two months. In contrast, etretinate requires more than two years for over 98% elimination, with minor quantities converting into etretinates, a process that accelerates in the presence of ethanol (Orfanos et al., 1997). *Replacement:* The Food and Drug Administration (FDA) approved asitretin in 1996 as a substitute for etretinate, which is no longer commercially available. Teratogenicity is the most serious adverse effect associated with oral retinoids, making the duration of these drugs in the body of significant clinical concern. Contraception is advised to be extended to two years in Europe and three years in America.

Adapalene

Adapalene is a synthetic, third-generation retinoid with its chemical structure derived from naphthoic acid. Its formulation involved the replacement of the unstable double bonds present in tretinoin with the aromatic rings of naphthoic acid. This process endowed adapalene with superior chemical and photostability, as well as high lipophilicity (Thiboutot et al., 2007).

In 1996, the Food and Drug Administration (FDA) granted approval for the use of adapalene in the treatment of acne vulgaris. Its classification under pregnancy category C necessitates careful evaluation of its use during pregnancy. The high lipophilic nature of adapalene allows for selective retention within the pilosebaceous unit, a feature beneficial in acne treatment.

Adapalene exhibits selective affinity for retinoic acid receptors (RARs) -β and -γ, compared to RAR-α. Its superior stability and photostability, relative to tretinoin, are notable. Moreover, its lower irritation profile permits combination with benzoyl peroxide (BPO). In terms of efficacy, adapalene mirrors tretinoin in managing conditions like verruca plana, keratosis follicularis, Darier's disease, Fox-Fordyce disease, photoaging, pigmentary disorders, actinic keratoses, and melanoma treatment.

Comparison studies indicate that the efficacy of adapalene at a 0.1% concentration in reducing comedones is comparable to tretinoin at 0.025% (Sudha & Pandi, 2021, p. 2). For non-inflammatory acne lesions, 0.1% adapalene exhibits a similar effect to 0.1% tretinoin. Generally, patients tolerate adapalene better, contributing to its acceptance in clinical practice.

Bexarotene

Bexarotene, a polyaromatic, third-generation retinoid, distinctively binds to Retinoid X Receptors (RXRs) with a binding potency approximately 100 times greater than that for Retinoic Acid Receptors (RARs). The clearance profile of bexarotene mirrors that of isotretinoin, and it has a terminal half-life of approximately 7 to 9 hours (Ghosal et al., 2016). Neither the parent compound nor its metabolites are excreted via urine, indicating a non-renal elimination route.

Metabolism of bexarotene occurs via the CYP3A4 pathway, predisposing it to significant drug interactions. Furthermore, it induces the generation of its own oxidative metabolites through hepatic CYP3A4 induction, which merits consideration in clinical use. Bexarotene's selective affinity for RXR receptors led to its approval for systemic use in

cutaneous T-cell lymphoma (CTCL) stages IA and IB in 1999, and subsequently for topical use in CTCL in 2000 (Väkevä, Ranki, & Hahtola, 2012) The therapeutic effects of bexarotene encompass the inhibition of cell growth, regulation of differentiation, and induction of apoptosis. It also exhibits immunomodulatory actions, reducing IL-4 levels, suppressing T-cell clonal proliferation, decreasing E-selectin, and curtailing T-cell trafficking to the skin.

Off-label uses of bexarotene extend to conditions such as hand eczema, psoriasis, and alopecia areata. Due to its teratogenic potential, bexarotene falls under pregnancy category X, contraindicating its use during pregnancy (Themes, 2019). Common adverse effects of bexarotene include skin redness, irritation, itching, and pain. Notably, the concomitant use of insect repellents containing DEET may exacerbate bexarotene toxicity. The typically recommended dose of bexarotene ranges from 300-400 mg/m2/day, administered once daily with meals. It is available in 10 mg and 75 mg tablets. Clinical response is usually observed within 4 hours, with superior outcomes in early stages of diseases. The relapse rates for conditions treated with bexarotene hover around 28% (Themes, 2019). Given the minimal renal elimination of bexarotene, judicious use is warranted in patients with hepatic impairment. Additionally, off-label use may be considered in conditions such as folliculotropic mycosis fungoides and lymphomatoid papulosis (Ghosal et al., 2016).

Tazarotene

Tazarotene is a third-generation retinoid used for the treatment of psoriasis and acne. It was the first topical retinoid approved by the FDA for psoriasis. The prodrug tazarotene is rapidly transformed into tazarotenic acid, its active metabolite, via cutaneous esterases. Its enhanced affinity for Retinoic Acid Receptors (RAR) β/γ over RARα, along with the absence of any affinity for Retinoid X Receptors (RXRs), distinguishes it in terms of selectivity (Khanna et al., 2022). Due to rapid metabolic transformation, systemic exposure to tazarotene is limited, thus minimizing potential systemic side effects (Essa Abd Elazim, Mahmoud Abdelsalam, & Mohamed Awad, 2022). Tazarotene modulates the pathogenesis of psoriasis at a molecular level by regulating the expression of retinoid-sensitive genes. These genes are instrumental in cell proliferation, differentiation, and inflammation – processes integral to the development of psoriasis (Khanna et al., 2022).

Tazarotene received approval from the FDA for the treatment of acne in 1997, followed by an endorsement for the treatment of psoriasis in 2000. The medication is commercially available as a 0.05% and 0.1% cream. Localized and perilesional irritation is the most common side effect observed in patients using tazarotene. Therapeutic efficacy of tazarotene has been found to improve when used in conjunction with topical corticosteroids in the management of psoriasis. Moreover, this combination provides a protective effect against steroid atrophy, an adverse event often associated with the long-term use of topical corticosteroids(Mehta & Amladi, 2011).Tazarotene is classified under pregnancy category X, signifying its potential teratogenic effects and contraindication during pregnancy. Comparatively, tazarotene and adapalene have demonstrated similar efficacy in the treatment of acne. However, adapalene generally induces less irritation, making it a more suitable option for patients with sensitive skin.

The utility of tazarotene in other skin conditions such as ichthyosis, mycosis fungoides, non-melanoma skin cancers, Bowen's disease, and onychomycosis remains underexplored, necessitating further investigation (Themes, 2019).

Trifarotene

The substantial therapeutic potential and distinct properties of trifarotene make it an exciting new fourth-generation retinoid. Additionally, trifarotene differentiates itself from other retinoids by exhibiting distinctive selectivity towards RAR receptors especially for RAR-gamma which easily binds over other retinoids (Cosio et al., 2021).The management of both facial and truncal acne in patients aged nine years or older got approval from the FDA for trifarotene use during 2019 (Tan et al., 2019). With the advent of trifarotene, the scope of retinoid utilization in the treatment of truncal acne has been considerably expanded, effectively addressing a previously unmet therapeutic need. Trifarotene's profile is further characterized by its improved tolerance, attributable to its unique ability to enhance skin hydration. This feature sets trifarotene apart from other retinoids and reduces the common side effect of skin irritation associated with retinoid therapy (Themes, 2019). The therapeutic potential of trifarotene extends beyond acne management, with the retinoid demonstrating a higher comedolytic effect than other commonly used retinoids, such as adapalene. Moreover, it exhibits a more potent reduction in pigmentation, broadening its potential use in managing hyperpigmentation disorders (Aubert et al., 2018).

Trifarotene's reduction of matrix metalloproteinase (MMP) activity suggests possible anti-ageing properties, and it has shown promise in not just treating hyperpigmentation and photoaging but also potentially slowing down the ageing process making it a valuable tool for dermatologists. The therapeutic effectiveness of trifarotene relies on its biological conversion into the active form of retinoic acid (RA) and owing to its inherent quality of being a lipophilic substance, it can effectively enter the epidermis and transform itself into RA. Trifarotene's prodrug status alongside its lipophilic character and low irritancy levels means that it can be used in cosmetic formulations without having to go through the process of obtaining FDA consent (Cosio et al., 2021).

Adverse Effects and Safety Concerns of Retinoids:

Retinoid usage can result in teratogenicity which causes both retinoic acid embryopathy and an increased likelihood for spontaneous abortion. In addition, decreased night vision ability and permanent dry eye issues are potential side effects for the ocular system from taking retinoids (Park, 2022). As well as this there’s an elevated risk to get infected with Staphylococcus aureus, hypercholesterolemia and hypertriglyceridemia which cause lipid disturbances are also notable(Beckenbach, Baron, Merk, Löffler, & Amann, 2015).

Milder side effects include xerosis, exacerbation of eczema-like skin irritations, hair loss, and pyogenic granuloma, an inflammatory skin lesion. Additionally, retinoid dermatitis can manifest as inflammation and cracking around the lips, known as cheilitis (Beckenbach et al., 2015; Fanjul et al., 1994). Management of these adverse effects often involves symptomatic treatment. For dry eyes, the use of artificial eye drops is recommended, while saline nasal spray can mitigate nasal dryness. Skin dryness can be treated with moisturizing creams and lotions, and lip balm can alleviate cheilitis. The use of sunscreen is also advised to prevent sunburn.

Retinoids can also affect the skeletal system, possibly causing diffuse interstitial skeletal hyperostosis (DISH), osteophyte formation, osteoporotic changes in long bones, and premature epiphyseal closure. Gastrointestinal side effects, including pancreatitis (associated with elevated triglyceride levels) and exacerbation of inflammatory bowel disease, may also occur.

A few instances of toxic hepatitis along with elevated transaminase levels were reported as hepatic side effects, while hypothyroidism is one of the common endocrine side effects associated with Bexarotene along with a controversial observation related to diabetes mellitus. Among the possible hematological side effects are leukopenia and agranulocytosis, while the potential for neurological side effects is present with both arthralgia-myalgia and pseudotumor cerebri (Duvic et al., 2001).

The teratogenicity of retinoids presents as a diverse range of anomalies, including craniofacial, central nervous system, cardiovascular, and auditory anomalies. Ocular anomalies such as microphthalmia and optic nerve atrophy can occur. Skeletal anomalies may manifest as an absence of clavicles or scapulae, aplasia or hypoplasia of long bones, a short sternum, sternoumbilical raphe, or absence of thumbs. Other anomalies may include thymic aplasia-hypoplasia and anal and vaginal atresia(Chiba et al., 2022).

Monitoring Patients on Systemic Retinoids:

Systemic retinoid therapy necessitates rigorous monitoring to safeguard patients from potential side effects and ensure optimal therapeutic outcomes. This involves a variety of tests and examinations, depending on the specific retinoid used (Alyamani et al., 2022). For isotretinoin and acitretin, an initial clinical examination forms the backbone of the monitoring process. In addition, several laboratory evaluations are critical, encompassing a complete blood count, liver function tests, and a lipid profile. These tests should be carried out prior to initiating treatment, then repeated at intervals of 4-6 weeks, and subsequently every three months (Alyamani et al., 2022; Themes, 2019).

Pregnancy monitoring is paramount given the significant teratogenic risk associated with these medications. This involves two negative pregnancy tests before treatment can be initiated. Thereafter, monthly monitoring is required, with pregnancy tests repeated at every visit. In amenorrheic patients, the second test should be carried out at least 11 days post sexual intercourse to ensure accuracy. Based on individual cases additional tests might also be mandatory. Potential skeletal side effects can be detected by monitoring through periodic hand-wrist and spine radiographs while ocular side effects should be detected with routine eye exams. After beginning therapy sessions it's important to attend check-ups every 90 days (Alyamani et al., 2022; Orfanos et al., 1997).

Patients taking bexarotene must have their thyroid functions checked regularly since it is associated with hypothyroidism. For the initial four to eight-week period of therapy, it's necessary for tests to be carried out once every two-week period. Upon completion of the first stage tests are required to take place every month for a 3-month period and then quarterly thereafter (Alyamani et al., 2022; Orfanos et al., 1997).

Conclusion

In conclusion, the implementation of retinoid therapies presents a broad spectrum of possibilities for the treatment of various dermatological conditions. It is imperative, however, to consider the associated side effects, potential for teratogenicity, and interactions when prescribing these medications. Each retinoid has unique characteristics, binding affinities, and modes of action that differentiate its therapeutic and adverse effect profiles. As with any potent therapeutic, monitoring is key in ensuring patient safety and optimizing clinical outcomes. This involves a rigorous schedule of clinical examinations, specialized tests, and laboratory evaluations, tailored to the individual retinoid and patient's needs. The meticulous adherence to

these monitoring protocols mitigates risks and contributes significantly to the successful deployment of systemic retinoids in dermatology.

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The Role of Vitamin D in Chronic Urticaria: A Comprehensive Review

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Definition, Epidemiology and Pathogenesis of Chronic Urticaria

Urticaria is a skin condition that results in erythematous and edematous lesions with itching sensations as well as a burning feeling which can disappear within 24 hours, and one symptom of angioedema is the sudden swelling of deeper skin layers along with accompanying mucous membrane involvement. This can be found alongside urticaria whose lifetime prevalence according to various studies ranges from 1% to 24% (Czarnetzki, 1989).

Classifying urticaria is determined by how long it lasts and whether there are any triggering factors. An episode which lasts less than 6 weeks will be classified as acute urticaria (AU), while those lasting for a period greater than this will be diagnosed as chronic urticaria (CU). Categorized into two types; one is the Chronic Inducible Uric aria(CIU), the other being Chronic Spontaneous Urticaria (CSU) (Zuberbier et al., 2014). Chronic urticaria (CU) is defined by recurrent episodes occurring at least twice a week for six weeks. If there are no apparent triggers causing it then it is classified as Chronic Spontaneous Urticaria and otherwise known as Chronic Inducible Urticaria when there exist triggers which trigger the outbreak (Benito-Villalvilla, Pérez-Diego, Subiza, & Palomares, 2021; Deleuran, 2015).

The etiological aspects of Chronic Spontaneous Urticaria (CSU) remain elusive in a significant 60-80% of cases. That being said, a plethora of potential triggers and causes have been identified, which encompass an array of medications, foodstuffs, additives, parasitic infestations, infections, and malignancies (Weller et al., 2013; Zuberbier et al., 2014). In addition, autoimmune conditions typified by chronic inflammation, and psychiatric comorbidities, also have been linked to CSU. The convoluted pathogenesis of urticaria is an area of ongoing exploration. The current body of research is increasingly illuminating the intricate dynamics between dysregulated immune response, mast cell activation, and the engagement of inflammatory mediators in the manifestation of the condition.

Even with the prevalent knowledge gaps, a handful of studies have endeavored to profile the clinical and epidemiological facets of chronic urticaria. Notably, recent research has indicated an incidence of about 1.8% among children, with a heightened risk observable among those residing in new abodes and originating from high-income families. The overall incidence of chronic urticaria shows variability across regions, ranging from 0.1-1.5 cases per 1000 inhabitants per year. The heterogeneity in these figures underscores the necessity for more in-depth, human-focused research to thoroughly comprehend this complex disease (Nettis et al., 2020).

Managing the impacts of chronic urticaria can be challenging due to its recurring nature and lack of clear cause, however, the precise cause for chronic urticaria is not fully comprehended and there are only a small number of studies that provide details on its clinical

and epidemiological profiles (Mariyath, Sukumarakurup, Pinky, Ajina, & Anagha, 2021; M. Shin & Lee, 2017). The presence of atopic diseases appears to be more common in children who experience chronic spontaneous urticaria than it does in the broader pediatric population, suggesting that there may be an underlying group or type of TH2-related chronic urticaria specific to these children(Roth et al., 2020). The link between thyroid autoimmunity and chronic autoimmune urticaria has been established as nearly %30-40 of CU patients have this type, however, limited research has been conducted on the etiology of chronic urticaria which hinders our comprehension of its clinical and epidemiological attributes (Cl & Kt, 2009a; Mariyath et al., 2021).

Various different factors play a role in causing chronic urticaria including metabolic health imbalances and environmental concerns alongside those related to immune function. Additionally, the development of it might be related to changes in the composition of the intestinal flora (GIURGIU, 2022; Matei et al., 2021). Autoimmunity related disorders such as CSU have been known to exhibit a correlation with specific types of autoantibodies like anti-cepsilonR1alpha or histamine-releasing antibodies which can activate mast cells resulting in the release of inflammatory mediators (Rojanapremsuk et al., 2015). This chronic urticaria is developed through a complex interaction between different types of cells including basophils and T-and B-Lymphocytes along with various mediators such as cytokines. Treatment for this condition currently involves addressing symptoms via non-sedating antihistamines or through medication that affect the immune system like omalizumab (Radonjic-Hoesli et al., 2017). However, a better understanding of the pathogenesis of chronic urticaria may provide a direction for developing more targeted and effective therapies in the future.

Vitamin D is an essential nutrient for maintaining health and a healthy skeleton as it forms an integral part of the bone metabolism, calcium, and phosphor homeostasis (Engelsen, 2010). Also has several other health benefits such as prevention or mitigation of cancer and autoimmune diseases, reduction in hypertension, and prevention of influenza (Engelsen, 2010). Recent research has identified the importance of vitamin D in regulating genes that have a wide variety of biologic functions that have been associated with vitamin D deficiency, such as cancer, autoimmune disorders, and cardiovascular disease (Hossein-Nezhad, Spira, & Holick, 2013). A recent study estimated the global reduction in mortality rates through the doubling of vitamin D levels, suggesting that improving vitamin D status may lead to significant health benefits (Grant, 2011). Although some negative effects have been attributed to an excess of sun exposure, solar radiation is a major source of vitamin D in humans, and vitamin D deficiency is associated with several diseases and conditions (Juzeniene et al., 2011). Moreover, a clinical review revealed that Vitamin D signaling is important in inflammation and cancer; molecular mechanisms and therapeutic implications (El-Sharkawy & Malki, 2020). Furthermore, Vitamin D is essential in regulating the calcium-phosphate metabolism. Additionally, it is widely used in human mental health as it regulates different functions in the central nervous system on neuronal development, neuromuscular function, inflammation reduction and enhanced immune response that have been linked to depression and other conditions (Kozyra et al., 2020).

Vitamin D Metabolism and Mechanisms of Action

Adequate vitamin D by synthesis in the skin or from dietary and supplemental sources is essential for health throughout life (Holick, 2008). Synthesis of vitamin D in the skin depends on the exposure to UVB radiation, and the levels of vitamin D synthesized vary according to factors such as skin pigmentation, latitude, season, and time of day (Chen et al., 2007). While

dietary sources of vitamin D, like oily fish and fortified foods, are also important, they provide only a portion of total vitamin D requirements (Grant & Garland, 2004).

The activation of Vitamin D receptors (VDRs) leads to initiation of intracellular signaling pathways within most cell types found in almost every tissue of the body including immune cells at (Remelli, Vitali, Zurlo, & Volpato, 2019), which results in VDR heterodimerizing with RXR. The resulting molecule is transported into the nucleus where it connects itself to Vitamin D response elements (VDRES) on DNA to regulate target gene expression (Larriba et al., 2013). Regulation of target gene expression occurs via interactions between transcriptional coactivators or corepressors and the VDR-RXR complex (Liu et al., 2021).

Vitamin D signaling is responsible for regulating the metabolism of calcium and phosphorus, but a new study has shown that it can also control the actions of immune cell activation by modulating cytokine or chemokine output. Thus, it can help regulate the body's inflammation and immune response (Dimitrov et al., 2020; Hasanloei et al., 2019). The promotion of IκB degradation due to Vitamin D Signaling can inhibit the NF-Kappa B Pathway leading to Anti-Inflammatory Effects and additionally VDR activation causes an increase in the expression levels of MAPK Phosphatase 5 which also has a part in reducing inflammation (Crescioli, 2021). Prostaglandin synthesis is suppressed by Vitamin D signaling via modulation of cyclooxygenases which helps in reducing inflammation and pain (Romney, Davis, Corona, Wagner, & Podrabsky, 2018).

Vitamin D has a modulatory effect on the immune system, including innate and adaptive immunity. One of the significant roles that vitamin D plays is its direct effect on T cell activation and antigen-presenting cells (APCs), specifically on dendritic cells (DCs)(Kamen & Tangpricha, 2010). Also influences the innate immune system by activating Toll-like receptors (TLRs) or increasing the levels of cathelicidins and β-defensins and the adaptive immune system by decreasing immunoglobulin secretion by plasma cells and the production of pro-inflammatory cytokines, modulating T cell function Vitamin D has the potential to suppress the overactive immune response as well as to enhance it to fight infections and diseases (Panfili et al., 2020; Sassi, Tamone, & D'Amelio, 2018).

Adequate vitamin D intake is essential for maternal and fetal health during pregnancy. However, epidemiological data indicate that many pregnant women have sub-optimal vitamin D levels, leading to adverse outcomes, such as preeclampsia, gestational diabetes mellitus, and bacterial vaginosis, and an increased risk for C-section delivery (J. S. Shin, Choi, Longtine, & Nelson, 2010).

Examining the entire genome has significantly aided in discovering more about the relationship between vitamin D and innate immune function. By using the VDR receptor alongside hydroxylase enzyme (CYP27B), Vitamin D's activated state - also named 125-(OH)2D3 - brings about its immunomodulatory effects. When facing a pathogen challenge macrophages express more VDR and CYP27B1, which plays a role in regulating the expression of cathelicidin gene necessary for creating an essential antimicrobial peptide that fights off bacterial infections (Chun, Liu, Modlin, Adams, & Hewison, 2014).

Vitamin D and Chronic Urticaria: Experimental Evidence

Several studies have shown the serum vitamin D levels in adults with CU are lower than those in healthy controls and showed a significant inverse relationship with urticaria activity scores, disease duration, and severity (M. Shin & Lee, 2017; Thorp, Goldner, Meza, & Poole,

2010). Notably, patients with critically low vitamin D levels (<10 ng/ml) were more likely to have chronic urticaria than patients with vitamin D levels ≥30 ng/ml (Woo, Jung, Koo, & Lee, 2015). But a study by Ozdemir et al., revealed the association of lower serum vitamin D concentrations with acute urticaria and an inverse relationship with disease duration in children (Özdemir, Köksal, Karakaş, & Ozbek, 2016).

Moreover, the effect of VDR gene FokI (rs2228570) polymorphism on the incidence of chronic spontaneous urticaria in the Chinese Han population is reported (Ma et al., 2020). Also, there is evidence of the possible role of vitamin D as a contributing factor in the pathogenesis of acute urticaria and a predictive marker for the disease activity in acute urticaria (Özdemir et al., 2016).

Vitamin D supplementation is a potential therapeutic option for CU patients and could lead to reductions in urticarial clinical symptoms (Li, Cao, Guo, Li, & Su, 2021). However, the role of vitamin D in the treatment of CU remains controversial. Therefore, there is a need for further research to establish the association between vitamin D status and CU.

The VDR gene contains SNPs that are associated with chronic disorders of an inflammatory and autoimmune etiology, type 1 and type 2 diabetes, colorectal adenoma, and tumorigenesis in various organs (Mohammed, Omar, Mohammed, & Deiab, 2017; Ogunkolade et al., 2002). VDR TaqI, BsmI, FokI, and ApaI gene polymorphisms have been linked to inflammatory diseases, and FokI polymorphism was associated with the incidence of CSU among Chinese Han populations (Ma et al., 2020). But VDR polymorphism does not seem to have any functional significance in CU.

Clinical Studies on Vitamin D Supplementation in Chronic Urticaria

Vitamin D supplementation can reduce the severity of urticarial symptoms, especially in adult patients with CSU(Izzah, Akhyar, & Abdiana, 2021; Li et al., 2021). Several in vitro and in vivo studies have suggested that vitamin D supplementation could improve urticaria symptoms; however, further research with larger samples is required before conclusive evidence is established. In a study conducted by Sindher et al. it was observed that daily consumption of cholecalciferol supplements resulted in an improvement in the urticarial symptoms experienced by one individual diagnosed with chronic uticaria, while the findings are optimistic, authors assert that more extensive investigations involving bigger populations are required before concluding if vitamin D supplements can actually mitigate the symptoms of patients with persistent episodes of hives and serve as a beneficial treatment option (Sindher, Jariwala, Gilbert, & Rosenstreich, 2012).

Özdemir et al reported that serum vitamin D levels decrease in children with acute urticaria, suggesting a potential role of vitamin D in pathogenesis and additive therapy in acute urticaria (Özdemir et al., 2016). Also Izzah et al conducted a literature study and found that vitamin D is a potential immunomodulatory that can be used as an alternative therapy for urticaria. A total of six studies with 621 chronic spontaneous urticaria (CSU) cases were included in their study (Izzah et al., 2021). Similarly, a systematic review and meta-analysis by Li et al reported that urticaria patients who received vitamin D supplementation experienced a significant improvement in clinical symptoms, particularly in adult patients with chronic spontaneous urticaria (Li et al., 2021).

The mechanism behind the positive effect of vitamin D supplementation in urticaria is not fully understood, but there is evidence to suggest that vitamin D supplementation has an

immunomodulatory effect. In their review article, Quirk et al suggest that the inverse relationship between vitamin D levels and urticaria severity could be caused by vitamin D's modulatory effect on dendritic cells and monocytes, which interferes with cytokine production (Quirk, Rainwater, Shure, & Gold, 2016).

Determining the best dosage level and timeframe for supplementing with vitamin D in cases of urticaria is difficult because prior research has used different amounts (between 600IU/d -to -4000IU) over various lengths (6-to -12-week intervals). However, available studies reveal that a range within vitamin D supplementation up to doses of around 4000IU safely treat urticaria while serving as an effective treatment especially among those with chronic spontaneous urticaria.

A randomized, double-blind, controlled trial by Rorie et al revealed improved urticarial severity scores following 12 weeks' supplementation of 4000 IU of vitamin D3 per day, regardless of baseline vitamin D status(Rorie & Poole, 2014a). In this study, fewer days with hives and better sleep quality were reported by participants who received vitamin D. Another study by Sayed et al compared two groups of CSU patients who received either high-dose (4000 IU/d) or low-dose (600 IU/d) of orally administered vitamin D3 for 12 weeks (Sayed, Abo-Ali, Sheha, & Eissa, 2017). The study concluded that the high-dose group had better Urticaria activity scores, Quality of life scores, and medication burden scores than the low-dose group.

The duration of supplementation in the trials varied from 6 to 12 weeks. Some researchers found that 12 weeks of vitamin D supplementation was sufficient to improve urticaria symptoms (Sayed et al., 2017; Yuan, Katari, & Shaker, 2019). In contrast, Lee et al found lower serum vitamin D associated with chronic urticaria symptoms, but the study did not investigate optimal doses or duration of treatment (Lee et al., 2017).

Potential Mechanisms of Action of Vitamin D in Chronic Urticaria

Studies have also shown decreased serum vitamin 25 hydroxyvitamin D levels in subjects with chronic urticaria (Rorie & Poole, 2014a). Its pathogenesis involves impaired immunocyte function, which might lead to the imbalance of regulatory T-cell cytokine production, an increase in circulating pro-inflammatory cytokines and worsening chronic urticaria (Woo et al., 2015). High vitamin D3 supplementation has also demonstrated symptom improvement when utilized as an add-on therapy in urticarial management (Rorie & Poole, 2014b).

While a number of literature has been produced about Vitamin D's effect on chronic urticaria leading to conflicting conclusions the true extent of its involvement in causing it particularly among children is yet to be determined, even though we are not completely sure how vitamin D functions when dealing with chronic urticaria, it is being used to manage autoimmune skin ailments such as vitiligo, and also psoriasis and atopic dermatitis (TR, 2019).

Mast cell activity appears to play a role in the pathogenesis of chronic urticaria, with approximately 30-40% of the patients exhibiting autoimmune mast cell activation (Cl & Kt, 2009b; Tedeschi, Lorini, Suli, & Asero, 2006). Mast cell and basophil activation results in the release of histamine and other pro-inflammatory mediators, which contribute to the development of urticaria symptoms. Vitamin D, along with other treatment options, may potentially alleviate urticaria symptoms by modulating mast cell activity (Cl & Kt, 2009b; Radonjic-Hoesli et al., 2017). According to a case report conducted by Yuan et al, prompt remission was observed in a patient with chronic urticaria after high-dose vitamin D repletion, following identification of vitamin D deficiency. The report also suggests that vitamin D may

promote the differentiation of CD4+ T regulatory cells and potentially slow down mast cell differentiation, although the precise mechanism of action remains unclear (Yuan et al., 2019).

Other treatments for chronic spontaneous urticaria include omalizumab, which binds to free IgE, downregulates FcεRI expression on mast cells and basophils, and reduces activation and symptoms (Coattrenec, Yasmine, Harr, Spoerl, & Jandus, 2020). Remibrutinib has shown inhibitory effects on the degranulation of activated mast cells and basophils in chronic urticaria patients (Gimeno et al., 2023). Furthermore, platelet activation has been identified as a potential indicator of disease activity, as platelet-derived factors may induce mast cell degranulation (Katayama, Matsui, & Murota, 2013). Understanding the mechanisms of mast cell activation and the treatment options that modulate it is crucial for improving outcomes in chronic urticaria.

The gut microbiota is a crucial factor in modulating the effect of vitamin D on human health (Singh, Rawat, Alwakeel, Sharif, & Khodor, 2020). Vitamin D supplementation has been shown to be beneficial in some patients with chronic urticaria (Rorie & Poole, 2014a), and its effects on the gut microbiota appear to be one of the possible mechanistic pathways. The gut microbiota is known to play a central role in the host's immune function and modulates the relationship between chronic inflammation and therapeutic outcomes in different diseases (Riccio & Rossano, 2017). Vitamin D has been shown to modulate the gut microbiota in cystic fibrosis patients , and its use is hypothesized to modify the microbiota in a beneficial fashion that may favorably influence chronic urticaria pathophysiology (Kanhere, Chassaing, Gewirtz, & Tangpricha, 2018). Additionally, Vitamin D is linked to chemopreventive effects such as CRC, and modulating the gut microbiota could be a potential mechanism of action (Rinninella, Mele, Raoul, Cintoni, & Gasbarrini, 2021). Vitamin D3 has been shown to increase T regulatory function, which can control inflammation and inhibit autoimmunity, indicating that the gut microbiota could be playing a role in chronic spontaneous urticaria and the efficacy of antihistamines (GIURGIU, 2022) Inflammation of the gut can alter the composition of the gut microbiota, with implications for the serum vitamin D level suggesting a complex interplay between the gut immune system, vitamin D, and the microbiota (Huang, Xiang, & Zhou, 2019). Overall, the interplay between vitamin D, the gut microbiota, and chronic urticaria is multifaceted and remains an area of ongoing research. Nonetheless, the current evidence suggests that the gut microbiota could be an important modulator of vitamin D's effect on chronic urticaria pathophysiology in some patients.

Conclusion and Future Research Directions of Vitamin D in Chronic Urticaria

The potential immunomodulatory capabilities of vitamin D, especially in the context of chronic urticaria, present an intriguing avenue for research. However, the precise underlying mechanisms remain to be fully unveiled. There is a pressing need for more exhaustive investigations to understand the exact role vitamin D plays in modulating immune responses, particularly how it influences cytokine production and inflammation. To validate the cause-and-effect relationship between vitamin D deficiency and chronic urticaria, we need robust, methodologically sound research designs, such as longitudinal and case-control studies. Additionally, the influence of vitamin D on mast cell activity is an area where considerable knowledge gaps persist. It's essential to illuminate the specific biochemical pathways involved in vitamin D's interaction with mast cells, and its subsequent effects on the differentiation of CD4+ T regulatory cells. Vitamin D supplementation has shown promise in ameliorating symptoms in some patients with chronic urticaria. As such, randomized controlled trials should be initiated to confirm the clinical efficacy of vitamin D as a therapeutic intervention, define

the optimal dosage and duration, and identify any potential adverse effects. The interplay between vitamin D, gut microbiota, and chronic urticaria is an intricate puzzle that needs to be solved. Deep diving into this complex relationship could yield insights into vitamin D's role in modulating the gut microbiota, and how these changes influence disease progression and treatment outcomes. Considering the variability in responses to vitamin D supplementation among patients with chronic urticaria, it may be beneficial to consider personalized treatment strategies. These could be based on genetic and metabolic markers, and aim to identify patient subgroups that might derive the most benefit from vitamin D supplementation. The role of vitamin D in pediatric chronic urticaria remains a contentious issue. As such, additional pediatric-specific research is warranted. Any such studies should take into account the unique physiological and metabolic characteristics of the pediatric population, to ensure appropriate and effective treatment modalities are proposed.

In conclusion, it can be asserted that the investigation of vitamin D's involvement in chronic urticaria presents a promising research pathway. However, there remains a considerable amount of work to be done in order to comprehensively explore its potential. The thorough comprehension of vitamin D's complex functions in immune modulation, mast cell activity, gut microbiota, and its utilization as a therapeutic intervention holds the potential to yield more efficient and precisely targeted treatment approaches for chronic urticaria.

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