MULTIDISCIPLINARY APPROACH IN MEDICAL SCIENCE IV

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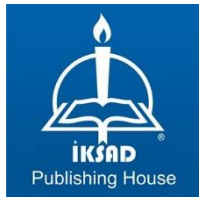

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CONTENTS

PREFACE

Since its existence, human beings have made great efforts to obtain accurate information. This effort continues today.

In parallel with the spread and development of communication tools, access to information has become easier. However, this situation also brought with it some problems. The most important of these problems is information pollution and confusion. Scientists make great efforts to convey correct information to people.

As in every field, serious studies are being carried out in the fields of medicine and health sciences. Scientists are trying to transfer correct information and produce innovative information by checking existing information. In addition to treating patients with accurate information in the field of medicine and health, they also contribute to the transfer of knowledge to the next generation.

We are happy to share our book "MULTIDISCIPLINARY APPROACH IN MEDICAL SCIENCE –IV", which contains valuable research in the field of medicine and health sciences, with the scientific world and our readers. I wholeheartedly congratulate our valuable writers who, in return for their great efforts, present their valuable works to the service of humanity.

I would like to thank the IKSAD Publishing family, scientific committee, authors and readers who contributed to the preparation, editing and publication of the book.

Assoc. Prof. Dr. Hüseyin KAFADAR

CHAPTER 1

PRECLINICAL AND CLINICAL USE OF ELLAGIC ACID: POTENTIAL EFFECTS AND APPROACHES

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INTRODUCTION

Tannins found in different plant species are polyphenolic compounds. These tannins, with molecular weights ranging from 0.5 to 20 kDa, are soluble in water (Khanbabaee & van Ree, 2001). Tannins are found in different parts of the plant. Their concentrations and compound diversities vary across plant species. Tannins are regarded as secondary metabolites and are classified into four categories. These are gallotannins, ellagitannins, condensed tannins, and intricate tannins (Khanbabaee & van Ree, 2001). These phytochemicals are in vacuoles within plant cells. When microorganism attacks occur, including viruses, bacteria, and fungi, they are released to prevent infection of plant tissues. Additionally, their preventive effect against insect invasions is well-known (Koide et al., 1998; Sepúlveda et al., 2011).

Recent studies suggest that oxidative stress plays a significant role in the complex neuronal pathology observed in neurodegenerative diseases (Halliwell, 2014). Reactive oxygen species (ROS) like hydroxyl (OH), superoxide anion (O_2^-), nitric oxide (NO), and hydrogen peroxide (H_2O_2) emerge as consequences of respiration and oxidative metabolism. Physiologically, it is in balance between ROS production and detoxification. This balance is maintained by the endogenous antioxidant defense system. Ellagic acid (EA) is an excellent scavenger of reactive oxygen species and has been shown to have potential in preventing neurodegeneration when chronically applied (Farbood et al., 2015; Kim et al., 2010).

The antioxidative capacity exhibited by natural compounds has served as a source of inspiration for the advancement of novel pharmaceuticals. Despite a decrease in drug discovery over the past decade, modern drug research has refocused on the field with the development of new techniques such as novel chemical combinations, high-throughput screenings, and metabolomics (Harvey et al., 2015). In fact, it is known that over 60% of the currently available drugs are derivatives of natural products (Nabavi et al., 2013). Moreover, the specificity of these compounds in cellular targets within biological systems, along with their broad chemical structural features and interactions with numerous receptors, further enhances the significance of natural compounds.

2. Ellagic Acid

First identified in gall nuts by Chevreul, ellagic acid was described by Braconnot in 1818 (Braconnot, 1818). He named the acid by reversing the word "galle" (Evtyugin et al., 2020). Ellagic acid, an inherent polyphenolic compound (2,3,7,8-tetrahydroxychromene), is frequently present in grape-like fruits, pomegranates, nuts, and various other medicinal plants. It possesses a molecular weight of 302.197 g/mol, a density of 1.67 g/cm³, and a melting point of 350°C. Due to its potential benefits for human health, ellagic acid compounds have garnered significant interest in recent years. Recent studies have highlighted ellagic acid's various pharmacological effects, including anti-diabetic (Raghu et al., 2016), anti-hepatotoxic (García-Niño & Zazueta, 2015), anti-cancer (Yousef et al., 2016), neuroprotective (Sarkaki et al., 2016), anti-obesity (Kang et al., 2016), anti-hypertensive (Dougan & Chekman, 2015), antinociceptive (Khatun et al., 2016), and antiviral (Park et al., 2014) activities.

2.1. Biosynthesis and Sources of Elajic Acid

Recent research has examined the chemistry and origins of ellagic acid. A summary of these characteristics will be provided in this study. Ellagitannins are typically formed through esterification of hexahydroxydiphenic acid with a sugar molecule, usually glucose.

The catalyzed hydrolysis of ellagitannins with acid leads to the release of hexahydroxydiphenic acid, resulting in the formation of ellagic acid. While raspberry, blackberry, and strawberry are the primary sources of ellagic acid, it is also abundant in hazelnuts, certain tree fruits, leaves, and barks. However, upon reviewing the literature, some inconsistencies in the reported quantities of ellagic acid can be observed.

While some authors document solely the concentrations of unbound ellagic acid, others present the complete content of ellagic acid. Additionally, the quantity of the compound significantly varies depending on factors such as harvest, seasonality, ripeness, hydrological conditions, and cultivation methodology.

2.2. Bioavailability and Metabolism of Elajic Acid

Numerous research endeavors have been carried out to investigate the metabolism of ellagic acid and ellagitannins (Ahmed et al., 2016; Espín et al., 2013; Landete, 2011; Larrosa et al., 2010). In summary, ellagitannins are

stable at gastric pH and do not hydrolyze into ellagic acid. The initial site of ellagic acid absorption is the stomach. However, for the formation of ellagic acid, ellagitannins need to be catabolized by intestinal microflora. In the intestines, ellagic acid undergoes metabolism through hydrolysis of lactone rings followed by decarboxylation, catalyzed by intestinal microflora, to produce urolithins (Espín et al., 2007; Gonzalez-Barrio et al., 2011).

Urolithins are produced through consecutive conjugation with UDP-glucuronosyl transferase (UGT) or sulfotransferases (ST) in the liver, followed by enterohepatic circulation. Ellagic acid undergoes methylation through the action of catechol O-methyl transferase (COMT), resulting in the formation of mono- and dimethyl ethers. Subsequently, these methylation derivatives are conjugated with glucuronides and sulfates. In many studies, ellagic acid has been reported to be rapidly absorbed in humans, reaching its maximum plasma concentration about an hour after administration. The maximum plasma concentration of urolithin, a derivative of ellagic acid, is typically reached around 24-48 hours after ingestion (Seeram et al., 2004; Stoner et al., 2005). Alongside dimethyl esters of ellagic acid, bioconjugates of urolithins A and B are present in the bloodstream and are transported to target organs.

2.3. The Reactions of Ellagic Acid

The reactions of ellagic acid can be grouped into three main categories. Firstly, it can undergo oxidation through interaction with reactive free radicals. Secondly, the nucleophilic hydroxyl groups of ellagic acid are involved in specific reactions. Lastly, ellagic acid can engage in electrophilic aromatic substitution reactions targeting its electron-rich aromatic rings.

Ellagic acid possesses notable free radical scavenging activity. Therefore, it prevents the harmful effects of reactive oxygen species, just as it inhibits lipid peroxidation. Marković and colleagues utilized density functional theory (DFT) for the analysis of substances in aqueous solutions (Marković et al., 2013). In aqueous solutions, ellagic acid loses a proton to free radicals through electron transfer, while in the gas phase or nonpolar solvents, it exhibits free radical scavenging activity through the transfer of a hydrogen atom to free radicals. In contrast, Galano and associates concluded that the hydrogen atom transfer mechanism occurs independently of the polarity of the environment (Galano et al., 2014).

The TAC of ellagic acid was initially assessed using the Trolox equivalent antioxidant capacity (TEAC) test. The Trolox equivalent antioxidant capacity quantifies the Trolox concentration needed to match the antioxidant capacity of 1 mM of the tested substance. In this investigation, standardized total pomegranate tannins, punicalagin, and ellagic acid were contrasted, yielding Trolox equivalents of 25.591, 100.90, and 40 μM, respectively. (Ahmed et al., 2016).

3. PRECLINICAL AND CLINICAL EFFECTS OF ELLAGIC ACID

3.1. Anti-inflammatory Effect of Ellagic Acid

Inflammation is an inherent mechanism that the body initiates as a reaction to injury, trauma, or infection (L. Chen et al., 2018). Inflammation is a crucial component of the immune system. Upon encountering damage or infection in any area of the body, the immune system undergoes activation. Immune cells are triggered to combat infection or repair damage (Fang et al., 2018). During the inflammation process, various chemicals and signaling molecules are released in the damaged or infected area, causing inflammation. This inflammatory response prevents further harm to the body and facilitates healing. However, prolonged inflammation, known as chronic inflammation, can become detrimental. Chronic inflammation may contribute to the onset of conditions like cardiovascular disorders, diabetes mellitus, cancer, and Parkinson's disease (Bartl et al., 2023; Gopinath et al., 2023; Mokgalaboni et al., 2023). Therefore, delving into the mechanisms that underlie chronic inflammation holds immense significance, as it has the potential to pave the way for novel treatments and strategies. Currently, drugs developed for chronic inflammation are primarily used for symptomatic relief. These often include NSAIDs and corticosteroids. These drugs can be employed for treating diseases involving chronic inflammation, such as arthritis. However, improper or long-term use of NSAIDs can lead to gastrointestinal ulcers, severe cardiovascular disorders, or the development of hypertension (Yasir et al., 2022).

In recent years, numerous studies have been published regarding the anti-inflammatory effects of ellagic acid (Hoang et al., 2023; Mazrooei et al., 2023; Xiong et al., 2023; T. Zhang et al., 2023). Consequently, due to its anti-inflammatory effects as part of a healthy, plant-based diet, ellagic acid can be utilized. Certain research investigations have suggested that ellagic acid might

have the capacity to reduce the susceptibility to chronic conditions such as cardiovascular diseases and cancer (BenSaad et al., 2017; Ridker, 2017). These effects could be attributed to its anti-inflammatory properties. To test this, Promsong and colleagues conducted an in vitro study using primary human gingival epithelial cells. Their study indicated that ellagic acid increased chemokine ligand 5, IL-2, and IL-1β. However, reducing the expression of IL-6, IL-8, and TNF-α (Promsong et al., 2015).

In recent times, several studies have indicated that inflammation contributes to the pathophysiology of depression (Miller, 2020; Zheng et al., 2021). Hence, there is potential for the use of anti-inflammatory agents in treating depression. A study based on the anti-inflammatory effect of ellagic acid revealed its anti-neuroinflammatory property (Mazrooei et al., 2023). Using a social isolation stress model, the study administered ellagic acid treatment to 48 mice. The findings indicated that ellagic acid decreased neuroinflammation in the hippocampus. Abnormal inflammatory responses are observed in certain respiratory diseases like asthma and COPD. This leads to excessive mucus secretion, bronchial hypersensitivity, airway obstruction, and impaired lung function (Cukic et al., 2012; Shen et al., 2018). Ellagic acid has been shown to reduce inflammation in eosinophilic asthma animal models. Ellagic acid is converted to urolithin A by gut microbiota. Urolithin A possesses anti-inflammatory properties. In a study testing this effect, inflammation was induced in A549 and dHL-60 cell lines, followed by treatment with ellagic acid and urolithin A.

Ellagic acid inhibited the levels of inflammatory cytokines and chemokines and decreased the expression of matrix metalloproteinase-9 in IL-1β stimulated A549 cells (Kim et al., 2023). Ellagic acid has shown anti-inflammatory properties in experimental models of ulcerative colitis. In an acute ulcerative colitis model in female Balb/C mice, animals were treated with ellagic acid alongside 5% dextran sodium sulfate (DSS) for 7 days. In another study using a chronic ulcerative colitis model, female C57BL/6 mice were given DSS for four weeks, followed by ellagic acid supplementation during a one-week recovery period. In the acute model, ellagic acid was shown to reduce IL-6, TNF-α, and IFN-γ, and improved disease severity. In the chronic model, ellagic acid suppressed disease progression and reduced intestinal inflammation (Marín et al., 2013). In a DSS-induced colitis model, ellagic acid taken in the daily diet reduced COX-2 and iNOS expression in the colon. This effect is significant as COX-2 and iNOS activation leads to

excessive production of inflammatory mediators that contribute to intestinal damage and inflammation (Rosillo et al., 2012). In a trinitrobenzenesulfonic acid-induced Crohn's disease model, ellagic acid reduced both COX-2 and iNOS expression. Ellagic acid use also decreased the production of myeloperoxidase and pro-inflammatory cytokines. Ellagic acid is likely to exert its effects via NF-κB. NF-κB activation triggers the expression of many pro-inflammatory cytokines including interleukins (IL-1, 2, 6, 8, 12) and TNF-α, contributing to the development and persistence of colon inflammation. NF-κB activation also regulates COX-2 and iNOS expression. Ellagic acid treatment significantly reduces NF-κB p65 nuclear protein expression in various diseases including ulcerative colitis and Crohn's disease (Derosa et al., 2016).

Hoang et al. employed a network pharmacology approach to reveal the anti-inflammatory effects of ellagic acid. In their study, they demonstrated that ellagic acid has interactions with fifty-two targets associated with inflammation. Topological analysis revealed important targets such as AKT1, VEGF-A, TNF, MAPK3, ALB, SELP, MMP9, MMP2, PTGS2, and ICAM1 (Hoang et al., 2023). In conclusion, ellagic acid, a naturally occurring polyphenolic compound, has the potential to be used as a therapeutic agent with anti-inflammatory properties. However, further research is needed to establish this conclusively.

3.2. The Anti-Cancer Effect of Ellagic Acid

Polyphenols exhibit their anti-cancer effects through antioxidant, anti-inflammatory, and anti-proliferative mechanisms. Furthermore, they influence subcellular signaling pathways, resulting in cell cycle arrest and the initiation of apoptosis (Harper, 2023). The anti-cancer properties of ellagic acid have been investigated in diverse human cancer cell lines, encompassing skin, esophageal, colon, and prostate cancers. These studies have shown that ellagic acid exhibits anti-proliferative activity, leading to cell cycle arrest and apoptosis (Larrosa et al., 2006). Ellagic acid is involved in various DNA repair reactions that prevent genomic instability leading to cancer when left unchecked (Xu et al., 2003). It exerts anti-proliferative effects and triggers apoptosis through mitochondrial pathways in Caco-2 cells while sparing normal colon cells (Larrosa et al., 2006). A study investigating ellagic acid's efficacy reported that it induced apoptosis in colon carcinoma induced by 1,2-dimethyl hydrazine, contributing to the maintenance of DNA repair reactions that sustain genomic stability (Umesalma & Sudhandiran, 2011). Ellagic acid

hinders the activation of PI3K/Akt, consequently modulating the Bcl-2 family proteins implicated in the intrinsic apoptotic pathway. Following ellagic acid treatment, an increase in Bax expression and caspase-3 activation resulted in elevated cytochrome c levels and subsequent cell death.

Prostate cancer is prevalent in men. In research conducted by Eskandari et al., the application of ellagic acid to prostate cancer cells resulted in diminished cell viability and the downregulation of STAT3, ERK, and AKT signaling proteins. Additionally, they reported a significant increase in IL-6 gene expression and IL-6 levels (Eskandari et al., 2016). Several studies have demonstrated that ellagic acid administration leads to increased levels of certain cytokines, such as IL-10 (Arulmozhi et al., 2013). Both ellagitannins and ellagic acid have consistently shown pro-apoptotic and inhibitory effects on cancer cells. They have suppressed PC3 xenograft growth in mice (Albrecht et al., 2004; Lansky et al., 2005). Ellagic acid isolated from five different plant species exhibited antiproliferative effects in human colon carcinoma cell lines (Stoner, 2009). González-Sarrías et al. documented that ellagic acid influenced phase I and II detoxifying enzymes in colon cancer Caco-2 cells (González-Sarrías et al., 2009).

The protective impact of ellagic acid on esophageal cancer was confirmed in a rat model of N-nitroso methyl benzylamine (NMBA)-induced carcinogenesis. Ellagic acid administration to rats reduced tumor incidence by 66.7% (Siglin et al., 1995). Ellagic acid-containing phytochemical products have been reported to have a chemoprotective effect against gastrointestinal system cancers (AL-Ishaq et al., 2020). In vitro studies have shown the effectiveness of ellagic acid against gastric cancer development. In vitro and *in vivo* studies have reported increased death of AGS cancer cells (Lim et al., 2019). Following ellagic acid application, a significant reduction in tumor size was observed in immune-suppressed mice carrying human gastric cancer tumors. The effect of ellagic acid was mediated through changes in apoptosis and inflammation-related genes, including blocking the production of proinflammatory cytokines (Cheshomi et al., 2021).

Hepatocellular carcinoma is one of the most malignant cancers. Treatment of HepG2 cells with ellagic acid led to an increase in apoptosis in G1 and a halt in mitosis (Qiu et al., 2021). Moreover, downregulation of p21 and MCM2-7 genes was reported (Ieda et al., 2021). In a separate research endeavor, the application of ellagic acid was found to impede the advancement of liver cancer by engaging Nrf2-mediated antioxidant pathways

(Bishayee et al., 2011). Urolitin A has reduced pro-apoptotic and inhibitory effects on cancer cells (Kujawska & Jodynis-Liebert, 2020). Ellagic acid triggers apoptosis through ROS formation in HepG2 cells, resulting in cell cycle arrest at the G2/M phase and diminishing the production of proinflammatory mediators (Das et al., 2017).

Furthermore, ellagic acid's positive effects on various cancer types such as pancreatic, lung, breast, and urogenital cancers have been demonstrated (Cota & Patil, 2023; Grijaldo et al., 2023; G. Lu et al., 2023; Meng et al., 2023; Ni et al., 2023; Vini et al., 2023).

3.3. The Effect of Ellagic Acid on the Liver

The liver has a crucial role in detoxification in the human body. However, this makes the liver vulnerable to toxins. Therefore, protecting the liver from these damages is of paramount importance. Compared to traditional and chemical drugs, natural products have a lower side effect profile (X. Lu et al., 2023). The antioxidant and anti-inflammatory properties of ellagic acid contribute to its hepatoprotective effects. Due to its antioxidant, anti-hepatotoxic, anti-cytotoxic, and antiviral features, ellagic acid assists in hepatic regulation.

Ellagic acid enhances the transcriptional activation of Nrf2, facilitating the elimination of reactive oxygen species. Additionally, ellagic acid has been reported to suppress liver cell damage induced by alcohol (Devipriya et al., 2007). In this study, alcohol-induced liver damage was created in rats and subsequently treated with ellagic acid. The study concluded that ellagic acid suppressed the toxicity caused by alcohol, corrected antioxidant conditions, reduced microcirculation lipid levels, and inhibited lipid peroxidation (Krishnappa et al., 2014; Singh et al., 1999). In a separate research endeavor, the addition of ellagic acid was found to decrease plasma cholesterol levels in rabbits with hyperlipidemia. It is possible that ellagic acid exerts an influence by either diminishing the function of 3-hydroxy-3-methylglutaryl coenzyme A reductase or enhancing the pace of lipid breakdown. Additionally, it could increase hepatic bile acid and fecal neutral sterol or reduce the levels of other lipids. Pathak et al. reported the antiviral activity of ellagic acid against HCV (Pathak et al., 2013). In this relevant study, ellagic acid was found to suppress the transcriptional activation of HBx, which is necessary for virus replication. Another investigation documented the ability of ellagic acid to inhibit NS3/4A protease activity in a

laboratory setting. This outcome was linked to the reversible interaction between ellagic acid and the Z-binding region of the enzyme (Reddy et al., 2014). Cisplatin has toxic effects on solid tumors and hematological malignancies (Dasari & Bernard Tchounwou, 2014; Tsang et al., 2009). Elevated oxidative stress has the potential to result in adverse effects such as nephrotoxicity, neurotoxicity, ototoxicity, and hepatotoxicity. (Gómez-Sierra et al., 2014; Nasr, 2014). Ellagic acid can reduce or reverse these effects (García-Niño & Zazueta, 2015; Yüce et al., 2007).

Cholestasis, oxidative stress, inflammation, and liver fibrosis are characteristic disorders. The impact of ellagic acid on liver damage induced by cholestasis was assessed using a rat model that involved bile duct ligation. The study concluded that ellagic acid reduced the levels of AST, ALT, ALP, and hepatic GGT (Widyawati et al., 2023). Liver diseases pose significant challenges for individuals with type 2 diabetes (T2DM). A study evaluating the hypoglycemic effect of ellagic acid and its impact on liver functions found that ellagic acid reduced blood glucose levels, lipid profiles, and inflammation in streptozotocin-induced T2DM rats. Another study reported that ellagic acid mitigated diabetes-induced liver damage (Farbood et al., 2019). By triggering AMP-activated protein kinase (AMPK) through AMP, ellagic acid diminishes de novo lipogenesis in both adipocytes and hepatocytes (Okla et al., 2015; Poulose et al., 2011; C. Zhang et al., 2019). Additionally, it has been shown to reverse hepatic steatosis by activating AMPK (ALTamimi et al., 2022). The involvement of liver pyruvate kinase (PKL) contributes to the progression of non-alcoholic fatty liver disease (NAFLD). Therefore, inhibitors of this enzyme have become a new treatment approach. In a study, ellagic acid was reported to inhibit PKL and reduce hepatic steatosis (Battisti et al., 2023).

3.4. The Antioxidant Effect of Ellagic Acid

Numerous studies have been conducted on the antioxidant stress activity of ellagic acid. Nevertheless, there has been limited research exploring the antioxidant properties of ellagic acid, primarily concentrating on its ability to neutralize free radicals. Ellagic acid's ability to scavenge free radicals has been reported through the activation of HPPH, halocarbon peroxyl, and hydroxyl radicals (Priyadarsini et al., 2002). Recently, Kılıç et al. demonstrated ellagic acid's scavenging effects on HPPT, ABTS, superoxide, and H2O2 (Kilic et al., 2014). Additionally, ellagic acid can form complexes with metal ions such as magnesium, calcium, manganese, iron, cobalt, and copper (Przewloka & Shearer, 2002). The proficient formation of metal

complexes by ellagic acid underscores its efficacy as an antioxidant, as it reduces the generation of free radicals caused by iron and copper ions (Perron & Brumaghim, 2009). Dalvi et al. conducted a study to explore the correlation between ellagic acid's iron-chelating capability and its potential to hinder in vitro oxyradical formation triggered by the interaction of ascorbate and Fe^{+++}. The study demonstrated that ellagic acid could complex with iron and thus prevent the formation of free radicals *in vitro* (Dalvi et al., 2017).

The antioxidant impact of ellagic acid on lung injury after intestinal ischemia has been studied (Dalvi et al., 2017). The study revealed that ellagic acid increased the total antioxidant capacity in lung tissue. Furthermore, histological tissue damage was lower in the group treated with ellagic acid. In a separate investigation, researchers explored the impact of ellagic acid on ischemia/reperfusion injury in skeletal muscles. In this study, ischemia was induced by tourniquet occlusion on the left hind leg of rats for two hours. Immediately after ischemia, the tourniquet was released, allowing for reperfusion of the area. Ellagic acid was orally administered starting one week before ischemia. After the experiment, it was observed that ellagic acid led to a notable reduction in antioxidant enzyme activity within the muscle tissue (Ekinci Akdemir et al., 2016).

Ultraviolet (UV) radiation plays a role in the formation of both melanoma and non-melanoma skin cancers. UV exposure leads to water hydrolysis and the production of ROS and RNS. These radicals react with proteins, DNA, RNA, and lipids, altering their structures. Antioxidants exhibit a protective effect against the impact of UV radiation. In a study, ellagic acid's antioxidant effect was demonstrated using a radiation dermatitis model in skin melanoma (SK-Mel-28) cells. Ellagic acid elevated the level of thiobarbituric acid reactive substances, which serve as indicators of lipid peroxidation, in SK-Mel-28 cells. They also reported a reduction in ROS production (Bose Subash Chandra Bose et al., 2023).

Yang et al. determined the antioxidant level of ellagic acid isolated from pomegranate peel (Y. Yang et al., 2023). They obtained 280 mg of ellagic acid from five grams of pomegranate peel. The obtained ellagic acid showed strong antioxidant activity with EC50 values ranging from 4.59 to 10.54 μg/ml. In another study, ellagic acid's antioxidant activity was tested in an oxidative damage model induced by H_2O_2 in PC-12 cell line, showing EC50 values of 92.14 and 36.70 μg/mL for OH^- and O_2^- radicals, respectively (Yulian & Xinyuan, 2023).

3.5. The Anti-Diabetic Effect of Ellagic Acid

Diabetes stands as a widespread endocrine disorder on a global scale. Given its antioxidant and anti-inflammatory properties, ellagic acid holds promise for ameliorating chronic conditions. Considering the studies, ellagic acid has shown positive results on HbA1c, insulin, TG, TC, HDL-C, MDA, GSH, CAT, SOD, TNF-α, and IL-6. These findings suggest that ellagic acid might exhibit an anti-diabetic effect by regulating glucose and insulin levels, dyslipidemia, oxidative stress, and inflammation (Ahmad et al., 2022; Altamimi et al., 2020; Polce et al., 2018; B. Zhou et al., 2019).

Ellagic acid appears to play an anti-diabetic role by increasing insulin secretion and sensitivity in pancreatic β-cells (Derosa et al., 2016). Administration of Emblica officinalis extract, which is abundant in ellagic acid, has been documented to exhibit a dose- and time-dependent reduction in fasting blood sugar levels in rats with diabetes (Fatima et al., 2015). In diabetic rats, the application of ellagic acid led to a noteworthy elevation in serum insulin levels. Similarly, the insulin/glucose ratio increased with Emblica officinalis treatment. After treatment with Emblica officinalis, immunostaining of the pancreas in diabetic rats showed an increase in the size and number of β-cells. Additionally, Emblica officinalis extract elevated TAC, GSH and TBARS. Chao et al. reported that ellagic acid increased insulin and decreased glucose levels in diabetic mice (Chao et al., 2009). Therefore, ellagic acid supplementation may contribute to the prevention or reduction of diabetic cardiomyopathy.

A meta-analysis evaluating the effectiveness of ellagic acid and its derivatives on diabetes included 13 preclinical and 11 clinical studies (Kwok et al., 2023). Preclinical studies revealed reductions in fasting glucose levels, total cholesterol, HbA1c, and LDL levels. However, no significant increase was observed in triglycerides, insulin, and HDL levels. In clinical studies, an increase in HDL and a decrease in HbA1c levels were observed. However, no significant differences were reported in total cholesterol, insulin, triglycerides, and LDL.

3.6. The Effect of Ellagic Acid on the Cardiovascular System

Cardiovascular disorders rank among the most prevalent illnesses globally, with a substantial proportion of fatalities being ascribed to sudden cardiac deaths. Ventricular arrhythmias are one of the causes of sudden cardiac deaths. This condition can arise from disrupted Ca++ signaling, ion

imbalances during myocardial ischemia, and excessive activation of the sympathetic system (Belevych et al., 2009). There is substantial evidence indicating that free radicals are significant mediators of ventricular tachycardia and ventricular fibrillation (Gelvan et al., 1991). Additionally, oxidative stress plays a crucial role in cardiovascular diseases, including tachycardia and fibrillation (Karagueuzian et al., 2013). Stress is one of the risk factors contributing to increased mortality. Elevated stress leads to myocardial ischemia and arrhythmia. Studies involving animals have demonstrated that stress can trigger hormonal imbalances, such as heightened levels of corticosterone and norepinephrine (Marin et al., 2007), as well as disruptions in the equilibrium between histamine and serotonin (Carnevali et al., 2012). Experimental studies indicate that chronic stress can initiate cell damage by increasing MDA, XO, and lipid peroxidation (Kaushik & Kaur, 2003). Many studies suggest that dietary polyphenols play a significant role in preventing arrhythmias and hypertension (Furuuchi et al., 2012; M. Kannan & Quine, 2013). The fact that ellagic acid is a polyphenolic compound that protects cells against oxidative stress is noteworthy. Studies have shown that ellagic acid positively affects cardiac muscle by enhancing calcium uptake into the sarcoplasmic reticulum and increasing Ca++-ATPase activity, resulting in a positive inotropic effect. Ellagic acid also inhibits several factors that reduce QRS complex voltage and induces a positive inotropic effect in the heart (Antipenko et al., 1999). Ellagic acid application in isoproterenol-induced myocardial infarction reduced heart rate, systolic and diastolic pressures, and led to increased levels of SOD, GPx, and CAT (M. M. Kannan & Quine, 2011). Polyphenolic compounds have been reported to bind to ß-adrenergic receptors, preventing increased heart rate (Zhu et al., 1997). Administering ellagic acid to rats before isoproterenol application reduced Q wave pathology and ST-segment elevation (M. M. Kannan & Quine, 2011). In another study, ellagic acid was found to diminish the levels of thiobarbituric acid reactive substances and lipid hydroperoxides in rats afflicted with isoproterenol-induced myocardial infarction. The study showcased that cerebral ischemia/reperfusion perturbed specific cardiac functions, and ellagic acid, known for its antioxidant properties, mitigated these impairments (Nejad et al., 2015).

Cardiac fibrosis is a disorder characterized by an increase in extracellular matrix and collagen fibrils in the interstitium. Oxidative stress plays a role in cardiac fibrosis development through TGF-β1. The efficacy of

ellagic acid was tested in a cardiac fibrosis model using the IM-HCF-1 cell line (Mannino et al., 2023). The study revealed that ellagic acid reduced profibrotic proteins and ROS. Additionally, it decreased TNF-α, IL-1β, and IL-6 level. Similar results have been reported in other studies (Li et al., 2023).

3.7. The Effect of Ellagic Acid on the Nervous System

Chronic neurodegenerative conditions associated with aging, such as Alzheimer's, Parkinson's, and multiple sclerosis, are predominantly attributed to the harm inflicted on macromolecules by ROS. (Forman & Zhang, 2021). The brain, which accounts for about 2% of body weight, has a significantly high oxygen consumption rate. ROS disrupt tight junctions and the structure of the blood-brain barrier (BBB) (S. Chen et al., 2022). Moreover, oxidative stress increases the risk of Alzheimer's disease by elevating amyloid β (Aβ) levels in the brain (Forman & Zhang, 2021). A study has revealed that metabolites of ellagic acid exhibit a capacity to decrease DYRK1A, resulting in reduced tau phosphorylation. This, in turn, contributes to the stabilization of microtubule polymerization (Tu et al., 2023). Additionally, these metabolites exhibited a neuroprotective effect by suppressing inflammatory cytokines induced by Aβ.

Under physiological conditions, ellagic acid is minimally metabolized in the stomach (Ahmed et al., 2016; Usta et al., 2013). Therefore, it holds potential as a phytotherapeutic agent for the development of neuroprotective drugs. While a definitive conclusion is not yet reached, ellagic acid is believed to cross the BBB (Kyriakis et al., 2015). The effects of ellagic acid on glial and neuronal cells have been studied *in vitro* (Spector & Johanson, 2014). However, based on bioavailability studies, it has been determined that some ellagic acid concentrations used *in vitro* may not be applicable *in vivo*. Therefore, this factor should be considered when conducting studies on the benefits of ellagic acid on glial and neuronal cells.

The effects of ellagic acid were investigated on cadmium-induced toxicity in primary rat astrocytes. (Yang et al., 2008). Cadmium poses concerns due to its impact on human health, causing tumors and neurological disorders, and contributing to environmental pollution. The study reported that ellagic acid increased cell viability and significantly prevented the ROS production induced by Cd2+ by acting as an antioxidant when applied at a concentration of 30 μM for 24 hours. While the protective effects of ellagic acid were demonstrated in this study, the molecular mechanisms were not

elucidated. However, ellagic acid's ability to chelate metal ions could potentially play a role in mitigating cadmium-induced toxicity.

While it has been reported that ellagic acid, when applied alone or in combination, suppresses Aβ-induced TNF-α secretion in primary murine cortical microglia cultures, the underlying mechanism remains undetermined (Rojanathammanee et al., 2013). Ellagic acid functions as an NF-kB inhibitor in the rat kidney, mouse liver to lung (E. Zhou et al., 2014), and oral ontogenesis in hamsters (de Oliveira, 2016). Furthermore, ellagic acid-rich pomegranate extract has been reported to suppress NF-κB activation in colonic immune cells in a Crohn's disease model (Rosillo et al., 2012). As mentioned in other studies, NF-kB plays a role in both inflammation and redox regulation (Salminen et al., 2011). It also participates in the regulation of SOD (Xu et al., 1999), thus stimulating NF-κB could enhance the activation of antioxidant enzymes (Sompol et al., 2006). Additionally, it would contribute to the regulation of pro-inflammatory cytokines (Yamamoto et al., 2001). In order to acquire data about the effects of ellagic acid on brain cells, *in vivo* studies have been conducted using various experimental models (Farbood et al., 2015). Preliminary evaluation of the data suggests that the *in vivo* neuroprotective effect of ellagic acid is attributed to its antioxidant properties

In a streptozotocin-induced diabetes model, it has been reported that daily administration of 50 mg/kg ellagic acid via gavage for 21 days protected the rat brain (cerebellum) and sciatic nerve (Uzar et al., 2012). Ellagic acid treatment also reduced STZ-induced lipid peroxidation and improved TOS and oxidative stress. Ellagic acid increased CAT and PON-1 enzyme activities. Similar effects were observed in the sciatic nerves of diabetic rats treated with ellagic acid. The exposure of STZ-treated rats to ellagic acid resulted in a decrease in neuronal hydrophobic degenerative changes, suggesting beneficial effects on brain structure. Ellagic acid treatment reduced hemorrhage and vascular damage in the rat brain. Although the exact mechanism remains not entirely elucidated, the involvement of PON-1, along with its antioxidant capabilities against lipid peroxidation, is believed to play a role in the neuroprotective effects of ellagic acid on the brain and nerves in rats. Farbood et al. investigated to determine whether ellagic acid could offer any advantageous effects in a rat model of traumatic brain injury (TBI) (Farbood et al., 2015). Daily administration of ellagic acid, started 7 days before brain lesion, was electrophysiologically examined and found to

effectively prevent TBI-induced memory impairment and improve neuronal functions. Additionally, ellagic acid mitigated the effects of TBI on pro-inflammatory cytokines IL-1β and IL-6. Another interesting finding is that ellagic acid protected the BBB from TBI-induced lesions.

Ellagic acid has shown protective effects against cerebral ischemia, which occurs in conditions such as cardiac arrest, asphyxia, and shock. Pretreatment of adult male Wistar rats with ellagic acid before occlusion prevents the reduction of blood pressure associated with occlusion. Ellagic acid pretreatment also reduces MDA levels and restores heart rate to physiological levels (Nejad et al., 2015). Rats experienced focal cerebral ischemia because of ellagic acid being directly injected into the middle cerebral artery (Pang et al., 2014). After a span of six hours following ellagic acid administration, a rise in neurological deficit score was noted. Furthermore, ellagic acid triggered a rise in cerebral infarct size, with the extent of increase being contingent on both dosage and duration. Treatment with ellagic acid resulted in a reduction of 2-aminofluorene N-acetylation (a carcinogenic agent) within cytosolic preparations obtained from the rat cerebrum, cerebellum, and pineal gland. In the same study, ellagic acid application reduced total aminofluorene and its metabolites in the pineal gland (Lin et al., 2000). Ellagic acid has demonstrated effects similar to those of antidepressants in mice exposed to the forced swim test or tail suspension test, suggesting potential antidepressant properties (Girish et al., 2012). To summarize, both acute and chronic administration of ellagic acid to mice seems to elicit anti-anxiety-like effects through interactions with the GABAergic system (Girish et al., 2012).

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CHAPTER 2

INVESTIGATION OF HIV/HBV/SYPHILIS COINFECTION AND LABORATORY RESULTS

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Introduction and Objectives

Human Immunodeficiency Virus (HIV) infection affects more than 38 million people worldwide. About 1.5 million new HIV infections were reported in 2021. Studies on HIV, a global public health problem, continue rapidly. In this study, Anti HIV(Snibe, MAGLUMI HIVAb/Ag X3, China) reactive detected and national AIDS validation center HIV-1/2 (Geenius HIV-1/2 Supplemental Assay, Bio-Rad Laboratories, Redmond, WA, USA) 119 HIV samples reported positive by The prevalence of co-infection with hepatitis B virus (HBV)/Treponema pallidum (Syphilis) and liver function tests (KCFT) were evaluated.

Materials and Methods

In our study, 119 HIV-positive patients who applied to our hospital between January 2018, and August 2023, were evaluated retrospectively. In the case of recurrent positivity, The first sample was included in the study. Demographic information, Venereal Diseases Research Laboratory (VDRL), Rapid Plasma Reagin (RPR)(Microcult, China), Alanin Transaminaz(ALT), Aspartate Aminotransferase (AST), and Alkaline Fosfataz(ALP) (Beckman Coulter AU5800,Germany) levels related data were analyzed. Detailed HBV(Snibe, MAGLUMI X3, China) serology and HBV DNA results were evaluated. HbsAg+ and HBV DNA levels above ≥1000 copies/ml were considered positive for HBV coinfection.

Conclusion and Discussion

When HIV-positive cases were examined, it was observed that all of them were HIV-1. While the frequency of HIV/HBV coinfection was 5.04%, The ALT and AST values of the same patients were found to be high. Median ALT:65.8U/L(Reference:0-50U/L) and median AST:57.4U/L(Reference:0-50U/L) one serum with coinfection with HBV and hepatitis delta virus(HDV) in which HBsAg and delta antigen were found to be positive together has been reported. When examined, it was observed that ALT and AST levels increased more than 2 times normal. This shows the severity of the damage in HIV/HBV/HDV coinfection. The samples 5.04%(n:6) with HIV/Syphilis coinfection were detected. HIV/HBV/Syphilis coinfection was detected in only 1 of these samples. For these samples, the median Treponema pallidum haemagglutination assay(TPHA) titer was 1/320. When analyzed by gender, HIV positivity in males was found to be higher at 95.7%. Detection of elevated ALT and AST levels in coinfection with HIV/HBV indicates the

severity of liver damage. No significant elevation was found in ALP levels. In HBsAg negative cases, it is possible to have HBV DNA positivity in mutant strains, it is possible to encounter HBV DNA in the presence of Anti HBs. However, the inability to detect these conditions is a limitation of our study. The protective role of the vaccine for HBV is obvious. We believe that the vaccine that can be developed for HIV is promising

KEYWORDS: Human Immunodeficiency Virus(HIV), Hepatitis B virus(HBV), Treponema pallidum(Syphilis), Coinfection

INTRODUCTION

HIV infection affects more than 38 million people worldwide. Approximately 1.5 million new HIV infections were reported in 2021. Studies on diagnosis and treatment for HIV, a global public health problem, continue rapidly. HIV/HBV coinfection is estimated to be 10% of the HIV-infected population worldwide. It has been reported that coinfection rates in HIV-endemic areas in South Africa are up to 25% (1). Higher HBV viremia levels, excessive immune reaction against HBV, liver cirrhosis, and rapid progression in hepatocellular carcinoma are reported in people co-infected with HBV and HIV (2,3).

HIV is an infectious disease that attacks the body's immune system, specifically white blood cells called CD4 cells. By destroying CD4 cells, HIV weakens an individual's immunity against infectious diseases such as tuberculosis and some cancers. People infected with HIV should be started on antiretroviral therapy (ART) as soon as possible after diagnosis. When treatment is continued in a controlled manner, transmission of HIV to other non-HIV-infected individuals can also be prevented. If the CD4 cell count falls below 200 in an HIV-infected individual, the individual's immunity is severely compromised and this condition is defined as acquired immunodeficiency syndrome (AIDS). The World Health Organization (WHO) continues its efforts to ensure that individuals with HIV risk have easy access to diagnostic tests (4).

In this study, we aim to determine the prevalence of coinfection in the region where our hospital is located in the last 5 years, and to determine whether there is an increase in the prevalence of HIV/HBV/Syphilis with the immigration of our country from neighboring countries and to determine the severity of liver damage in coinfection.

MATERIAL AND METHODS

The serum of 119 HIV-positive patients admitted to our hospital between 1 January 2018, and 1 August 2023 was evaluated retrospectively. Routine laboratory records were reviewed. In the case of recurrent positivity, which was reported as positive by the National verification center for HIV, the sample at the first application was included in the study. Demographic information, Venereal Diseases Research Laboratory (VDRL) and Rapid Plasma Reagin (RPR) (Microcult, China), Alanine Transaminase (ALT), Aspartate Aminotransferase (AST), and Alkaline Phosphatase (ALP) (Beckman Coulter AU5800,Germany) levels related data were analyzed. Detailed HBV serology (Snibe, MAGLUMI X3, China) and HBV DNA results were evaluated. HbsAg+ and HBV DNA levels above ≥1000 copies/ml were considered positive for HBV coinfection.

ALT, AST, and ALP levels of 119 HIV-positive patients who were reported as positive by the HIV-1/2 (Geenius HIV-1/2 Supplemental Assay, Bio-Rad Laboratories, Redmond, WA, USA) differential test by the National AIDS Confirmation Center were evaluated.

Hepatitis B virüs(HBV)

HBV is an important life-threatening global health problem. More than 240 million of the two billion infected people are chronic carriers. WHO estimates that 296 million people lived with chronic hepatitis B infection in 2019, with 1.5 million new infections each year. An estimated 820,000 deaths were reported in 2019, mostly due to hepatitis B-related cirrhosis and hepatocellular carcinoma (5).

Studies have been reported showing that the prevalence of HBV is significantly higher among HIV-positive individuals due to common transmission routes and common risk factors (6,7). HIV generally accelerates the natural history of HBV infection and facilitates faster progression of liver disease to cirrhosis and hepatocellular carcinoma (HCC) (8).

Traditionally, HBV is diagnosed by serological techniques to detect antigens or antibodies. Hepatitis B surface antigen (HBsAg) is often used for routine diagnosis as it is considered the hallmark of infection. During acute infection, antibodies against HBV core antigens (anti-HBc) (both IgM and IgG initially) appear 1-2 weeks after the appearance of HBsAg, while IgG

persists during chronic infection. The presence of antibodies against HBsAg (anti-HBs) represents immunity against HBV infection (9).

Treponema pallidum(Syphilis)

Syphilis, Treponema pallidum subsp. pallidum can be transmitted transplacentally, mainly sexually, and by blood transfusion (11,12). Although it is a notifiable disease in our country, it is difficult to estimate the true frequency of the disease due to the problems in the notification system. It is stated that the incidence is increasing especially in HIV-positive individuals in developed countries (10,13). Since it cannot be produced in culture, mainly serological methods are used in diagnosis. Nontreponemal tests; VDRL and RPR are flocculation-based tests that detect non-specific antibodies against cardiolipin, lecithin, and cholesterol antigens (14). Tests that detect specific antibodies against T. pallidum antigens (TPHA), TPPA (T. pallidum Particle Agglutination Assay), FTA-ABS (Fluorescent Treponemal Antibody Absorption), and ELISA (Enzyme-Linked Immunosorbent Assay) are used as treponemal tests (15,16).

Today, different applications are used in the understanding of syphilis. These should be used for screening in non-treponemal tests in conventional screening and positive results should be confirmed with treponemal tests (18). Another update, identified as reverse software, uses treponemal tests in the "European Center for Disease Prevention and Control" (ECDC) screening, and positive results are confirmed by a different treponemal test (17). Treponemal tests are tests with high specificity and are used for verification in the conventional algorithm and for both screening and verification in the reverse algorithm. Although nontreponemal tests can be used in treatment follow-up, treponemal tests are not used in treatment follow-up because they can remain positive for life (15,18). Non-troponemal test false positive Pregnancy, Tuberculosis, Rickettsial infection, Non-syphilis treponemal infections, endocarditis, Immunizations, Malaria, IV drug use, autoimmune diseases, chronic liver disease, underlying HIV disease. False negativity of non-tropenamal tests is the Prozone event and early treatment. It can be seen in cases such as the test becoming negative over time. It can be caused by reasons such as hepatitis C. The false positivity rate is lower in treponemal tests compared to nontreponemal tests. Positive nontreponemal test results need to be confirmed by treponemal tests. False positivity detected in treponemal tests; technical problems, intravenous drug use, pregnancy, non-pathogenic Treponemas, Borrelia species that can cause cross-reactions

and different autoimmune diseases. False-negative results are not common in treponemal tests (19).

CONCLUSION

It was determined that all HIV-positive cases were HIV-1. Because HIV 1 can be seen more frequently and we are not in the endemic region. While HIV/HBV coinfection rate was 5.04% (n=6/119 in HBsAg+ and anti-HBc IgG- samples), HBsAg and anti-HBs positivity were not found together. ALT and AST values are also high in the same patients. Median ALT: 65.8U/L (Reference:0-50U/L), median AST:57.4U/L (Reference:0-50U/L), and median age range 37.3. It was reported that HBsAg and delta antigen were positive together in 1 serum with HBV and Hepatitis Delta virus (HDV) co-infection. When this serum was examined, it was observed that AST and ALT values were 2 times higher than normal values. This indicates the severity of the damage in HIV/HBV/HDV coinfection. HIV/Syphilis relationship was detected in N=6 (5.04%) samples. HIV/HBV/Syphilis coexisted in only 1 of these samples. The mean TPHA titer of these HIV/Syphilis co-infected samples is a median of 1/320. When examined by gender, HIV positivity in men is higher with a rate of 95.7% (n=114). Detection of ALT and AST levels higher than the reference range in coinfection with HIV/HBV indicates the severity of the disease. No difference was detected at the ALP level. European guidelines recommend that sexually active HIV-positive homosexuals be screened for HBV, HCV, and syphilis at the time of HIV diagnosis and at least annually thereafter (20). In addition, German guidelines recommend vaccinating sexually active homosexuals and other immunocompromised persons against HBV (21). However, HIV-positive individuals are less likely to develop effective immunity against HBV because their immune response is inadequate (22,23,24,25,26,27). In HBsAg negative cases, it is possible to observe HBV DNA positivity in mutant strains and to detect HBV DNA in the presence of Anti HBs. However, the inability to detect these conditions is a limitation of our study. The protective role of the vaccine against HBV is clear. We believe that the vaccine developed for HIV is promising.

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to declare.

Author contributions: FMA Generated the

Initial idea and experimental design FMA

Performed the experiments and analyzed data.

FMA: Wrote the manuscript. and gave final approval to the submitted version

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CHAPTER 3

ARE THERE ANY INNOVATIONS IN THE TUBERCULOSIS LABORATORY?

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INTRODUCTION

Tuberculosis, one of the oldest known diseases in the world, continues to be a serious public health problem in many countries. Early diagnosis of active disease is imperative for effective patient management. Clinical diagnosis should be supported by microbiological diagnostic methods. Tuberculosis laboratories have always played a critical role in drug susceptibility testing as well as tuberculosis diagnosis. Traditional diagnostic methods continue to be used in many laboratories. In recent years, the use of new methods that allow earlier diagnosis and drug susceptibility test results have become widespread.

Mycobacteria are the causative organisms for diseases such as tuberculosis (TB) (Forbes et al, 2018). TB is an infectious disease with high morbidity and mortality worldwide. Pertinent laboratory systems being reachable for fast and rigorous disease diagnosis is required to achieve tuberculosis detection and prevention. World Health Organization (WHO) received reports of 10.6 million new/recurrent TB cases and 450 000 multi-drug resistance (MDR) or rifampicin (R) resistant cases in 2021. Only 55% of cases with pulmonary tuberculosis have been confirmed by bacteriological methods. Only 51% of cases with bacteriologically confirmed pulmonary tuberculosis were tested for R resistance. While the rate of confirmation of TB cases by bacteriological methods is 80% in developed countries, which have most of the diagnostic methods, this rate is approximately 50% in countries with limited diagnostic possibilities (WHO, 2022).

This data shows that the availability of diagnostic methods should increase in countries with limited resources. Microbiology laboratory needs to answer two main questions quickly and reliably in patients with clinically suspected TB; was M. tuberculosis detected in the patient sample? and ıf M. tuberculosis is detected, which drugs is the strain resistant to? (Somoskovi and Salfinger, 2019).

TB laboratories in our country and their characteristics were published in the 2020 Report on Tuberculosis in Turkey. Laboratories are divided into three levels according to this report as the laboratories that only do smear microscopy (Level 1), smear and culture (Level 2), and smear, culture and drug susceptibility testing (IDT) (Level 3). National Tuberculosis Reference Laboratory under the General Directorate of Public Health and of the 270 TB laboratories across the country, 53.0% are Level 1, 22.6% are Level 2, and 24.4% are Level 3.

In addition, Mycobacterium tuberculosis complex (MTBC)-non-tuberculosis mycobacteria (TDM) differentiation is performed in 85 laboratories, molecular diagnosis is performed in 59 laboratories and rapid resistance testing is performed in 19 laboratories (Türkiye'de Verem Savaşı

Derneği 2020 Raporu, 2021). A global project was initiated in 1994 under the leadership of WHO to monitor TB drug resistance in the world. All countries within the scope of this study have started to establish their own drug resistance surveillance systems (Zignol et al, 2012). Tuberculosis Laboratory Surveillance Network (TuLSA) project in which the course of drug-resistant TB cases is monitored, the resistance load is determined, the quality and capacities of TB laboratories are determined was initiated by the Ministry of Health, Türkiye in 2011 (Sezen et al, 2015).

This project is still continuing as the Turkish National Tuberculosis Surveillance Survey (TUTSA) and its results are presented in the tuberculosis reports (Türkiye'de Verem Savaşı Derneği 2019 Raporu, 2020). Turkey is not among 30 countries which have high disease burden in terms of the multidrug resistant (MDR)-TB. The estimated rifampicin resistance (RD)/MDR-TB rate is 3,5% in the new cases, while in the previously treated cases is 12%.

In this article, we will examine the examinations made in the TB laboratory under the following titles:

I. Microscopy;
1. Carbol fuchsin method, hot (Ziehl-Neelsen)
2. Carbol fuchsin, cold (Kinyoun)
3. Fluorochrome method (Rhodamine B+ Auramine O/Auramine O)

II. Decontamination Methods
III. Culture;
1. Solid Based,
2. Liquid Based

IV. Identification
V. Molecular Tests
VI. Tests for Susceptibility to Antituberculosis Drugs

I.MICROSCOPY

Evaluating smears of clinical specimens under a microscope is a fast and inexpensive screening method. The mycolic acid in the Mycobacterium spp. cell wall allows it to be distinguished from other bacteria. Mycobacteria are resistant to decolorization with acid and alcohol due to their structure. Therefore it is called “acid-fast bacillus” or “ARB”. However, the sensitivity of ARB methods, a rapid TB screening test, is low (44% in new TB cases, 15-20% in children) (Lange and Mori, 2010). Three main methods are commonly used for ARB smears. Light microscopy is used to examine in the Ziehl-Neelsen and Kinyoun methods while fluorescent microscopy is used in the fluorochrome staining method. Auramine O is used alone or with rhodamine B in the fluorochrome staining method (Forbes et al, 2018). Fluorescent microscopy is more expensive than conventional light microscopy. However, the advantages are that the dye protocol is simpler, it does not require heating and reads the divisions faster. Hence it is recommended to be used in large laboratories with large number of samples (Martinet al, 2019). WHO recommendations after 2009 are in favor of Auramine staining except for the traditional Ziehl-Neelsen light microscope (WHO,2011).

The total clinical smear sensitivity differ between 20-80% depending on mycobacteria load, the natüre of ARB staining used and the laboratory technician expertise (Steingart et al, 2006). Smearing the samples after the decontamination-homogenization process increases the sensitivity (Forbes et al, 2018).

Current guidelines in Turkey recommend microscopy of three consecutive sputum samples for pulmonary tuberculosis diagnosis (Kara, 2019). On the other hand, WHO recommended 2 ARB smears as opposed to 3 smears because evaluation with a third smear has been reported to contribute only 3.1% if the first two smears are negative (WHO, 2007; Mase et al, 2007).

II.DECONTAMINATION METHODS

Mycobacteria are slow growing microorganisms. Contamination of samples with faster growing bacteria may prevent detection of mycobacteria grown in culture. Therefore, samples must be processed to reduce the contaminated bacterial load without adversely affecting mycobacterial viability before culture. Laboratory contamination rates must be within a certain range. Sodium hydroxide (NaOH) AND N-acetyl-L-cysteine (NALC) are the most commonly used agents in these procedures for non-sterile samples (Forbes et al, 2018). Studies are carried out that use different agents (Chlorhexidine, etc.) other than traditional methods or that eliminate the need for solution preparation and centrifugation and aim to shorten the processing time (Sharma, 2012; Asmar and Drancourt, 2015; Rivas, 2010; Ganoza, 2008)

Absorbent beads have also been used in decontamination and condensation processes. The process has become much easier with the elimination of the centrifugation process and its duration is shortened. However, there are studies reporting that the isolation rate is slightly lower in samples processed with this decontamination kit (Karakece et al, 2014).

III.CULTURE

The gold standard in TB diaognosis is accepted as culture method. Solid (egg and agar-based), liquid and automated liquid culture systems are used for culture (Surucuoglu, 2003).

III.I. Solid media: Löwenstein-Jensen (LJ), the most persistenlty used media in routine laboratories, is egg-based. LJ medium supports the MTBC growth of (Forbes et al, 2018). The duration of becoming visible in cultre for MTBC and TDM strains is several weeks because of their slow growth in LJ medium. Therefore, the plates are kept for six to eight weeks before being disposed of and specified as negative (Simner, 2016). Agar-based media (Middlebrook 7H10 and Middlebrook 7H11) are also used for the production of mycobacteria. MTBC colonies become visible approximately 10-12 days earlier on agar-based media compared to LJ medium (Surucuoglu, 2003).

III.II. Liquid media: These are the media that give faster results and have higher isolation rates compared to solid media. Subculture, IDT and biochemical tests can be performed with Middlebrook 7H9 while Dubos Tween-al-bumin broth is used for subculture and IDT susceptibility testing studies (Forbes et al, 2018). Liquid automated culture systems have high sensitivity in the early diagnosis of TB and offer the advantage of giving results in a shorter time. Commercial culture systems used today are BACTEC Mycobacteria Growth Indicator Tube (MGIT) 960 (Becton Dickinson), VersaTREK Culture System II (Trek Diagnostic Systems, Cleveland, OH) and MB/Bact Alert 3D System (bioMérieux). The results of numerous studies have shown that these systems can be used as the gold standard for TB diagnosis (Forbes et al, 2018). The equipment steadily oversee tube fluorescence, permitting laboratory personnel to rapidly determine positive tubes and start the assignment of seeking out mycobacteria existence. It has high sensitivity compared to solid culture in addition to faster reproduction. In a meta-analysis comparing the MGIT 960 system with LJ medium, its sensitivity in identifying mycobacterial species was found to be higher than LJ (81.5% for MGIT, 67% for LJ) and it was shown that the sensitivity of the system increased (87.7%) when used with a solid medium (Cruciani et a, 2004). Yazsiz et al. compared LJ culture and MGIT 960 liquid culture methods in a study they conducted with a large number of samples (Ganoza et al, 2008). Their sensitivity and specificity were 92% and 98% for LJ medium, respectively; 96% and 99% for MGIT 960. In addition, the mean

growth time in the study was calculated as 24.5 ± 7.3 days for LJ culture and 10.4 ± 5.3 days for MGIT 960. It has been reported that the most important advant age of the MGIT 960 system is that it gives results in a short time (Yazisiz et al, 2019). Gas pressure changes due to the metabolic activities of microorganisms are observed in the VersaTREK system, (Yuksel et al, 2011). A colorimetric carbon dioxide sensor is used in the MB/BacT Alert 3D system (Whyte et al, 2000).

IV.IDENTIFICATION

Conventional methods are based on bacterial growth rate, growth temperature, colony appearance, pigment production and biochemical properties. Although these methods are time consuming and difficult to implement, their costs are considerably lower than newer methods and they are still valid in the identification of TB bacilli.

Mycobacterium species are subdivided primarily according to their growth characteristics (reproduction rate, growth temperature, pigment formation, colony morphology). Then, definitive diagnosis is made on a species basis using biochemical tests such as niacin accumulation, nitrate reduction, catalase, pyrazinamidase, growth in a thiophene-2-carboxylic acid (T2H) medium (Karakece,2014). Rapid identification of cultured samples can be made by molecular methods. Molecular methods are difficult to obtain in every laboratory because they are expensive compared to conventional methods. It is recommended to send positive cultures to a reference public health laboratory if these tests are not available, (Warshauer et al, 2019). The MGIT 960 system allows species identification with para nitrobenzoic acid (PABA). It has been reported that the MGIT 960 system is a fast and convenient method for the MTBC identification with PNBA (Rodrigues et al, 2009).

V.MOLECULAR TESTS

Molecular methods are an alternative to conventional methods in MTBC identification and IDTs (Rodrigues et al, 2009). Most molecular tests rely on the detection of MTBC-specific nucleic acids in both DNA and RNA using amplification techniques such as polymerase chain reaction (PCR). It also allows the detection of gene mutations associated with drug resistance (Dicks and Stout, 2019).

Two nucleic acid amplification tests (NAATs) have been approved by the FDA for detection of MTBC directly from clinical specimen;

1. Gen-Probe Hologic Amplified Mycobacterium tuberculosis Direct test" using transcription-mediated amplification method,
2. "Cepheid Xpert MTB/R test" using real-time PCR method (Whyte et al, 2000; Nurwidya et al, 2018).

V.I.Gen-Probe Hologic Amplified Mycobacterium tuberculosis direct test:

Its use in processed sputum samples (smear positive or negative) and bronchial and tracheal aspirate samples has been approved by the FDA (26). The sensitivity, specificity, positive and negative predictive values of the MTD (Mycobacterium tuberculosis direct test) Gene-Probe® method were found to be 89%, 100%, 100%, and 93%, respectively (CDC, 2013) in a comparison with the BACTEC MGIT 960 system and LJ medium.

V.II. Xpert MTB/R Testi: The GeneXpert MTB/R assay (Cepheid, Sunnyvale, California, USA) is a probe-based, fully automated PCR assay that simultaneously detects MTBC identification and R resistance (rpoB) (Rodrigues et al, 2009). The test has FDA approval for use in smear-positive and smear-negative samples made from direct and processed sputum samples (Whyte et al, 2000). The sensitivity of the Xpert MTB/R test is higher in smear-positive samples than in smear-negative samples (Kunduracıoglu et al, 2013). Results should be interpreted with caution, as it cannot distinguish between live and dead bacilli. The disadvantages of the test are its low sensitivity and high cost in cases with lower bacillus levels such as in extrapulmonary TB cases (Rodrigues et al, 2009). NAATs including the Xpert MTB/R test are more sensitive and specific than microscopy alone for MTBC detection of MTBC (Nurwidya et al, 2018). The Center for Disease Control and Prevention (CDC) Xpert, who previously recommended three consecutive negative sputum ARB smear results to remove respiratory isolation, stated that the MTB/R result was sufficient evidence to exclude pulmonary tuberculosis (CDC, 2013). Afşar et al. compared the performance of the GeneXpert MTB/R (GX) (Cepheid, Sunnyvale, California, USA) test with culture as a reference method, sensitivity and specificity as % in respiratory samples, respectively. 100 and 99%; found 87% and 99% in non-respiratory samples (Chakravorty et al, 2017) in a study they conducted on 790 clinical samples taken from patients clinically suspected of having TB in İzmir (Chakravorty et al, 2017). Sensitivity and specificity of GeneXpert MTB/R were similar in lung and extrapulmonary samples (78.2% vs 90.4% for lung, 79.3% vs 90.3% for extrapulmonary TB) in another study evaluating the performance of the GeneXpert MTB/R assay in the diagnosis of extrapulmonary TB (Afsar et al, 2018). It has been reported that the Xpert MTB/R Ultra (Ultra; Cepheid) test in respiratory samples taken from children helps in the rapid and accurate diagnosis of pulmonary tuberculosis (Mechal

et al, 2019; Zar et al, 2019). Anyplex MTB/NTM test is a fast, practical and reliable test that can be used in the diagnosis of routine TB (Alp and Saribas, 2019). Culture methods (LJ and BACTEC MGIT 960) and molecular methods [COBAS TaqMan 48 MTB Kit (Roche Diagnostics GmBH, Mannheim, Germany) and 85B mRNA-based real-time PCR it] were compared in another study using sputum samples. The sensitivity and specificity of the molecular assays were 93.3% and 83.3% for the COBAS TaqMan MTB Test; 98.3% and 95.0% for real-time PCR based on 85B mRNA. It has been reported that real-time PCR method targeting the 85B gene is a more useful and faster technique for the detection of M. tuberculosis bacillus (Demirci et al, 2018).

V.III. Nucleic acid hybridization probes: Nucleic acid hybridization probes (AccuProbe; Hologic/Gen Probe, Marlborough, MA) can identify MTBC, M. avium complex, M. gordonae, M. intracellulare, and M. kansasii from culture. It has the advantage of identifying mycobacteria grown in culture and giving results within two hours (Brown-Elliott and Wallace, 2019).

V.IV. MALDI-TOF MS: Vitek MS (BioMérieux, Durham, NC) is approved by FDA approval to determine mycobacteria among the present MALDI-TOF MS systems while MALDI Biotyper (Bruker Daltonics, Billerica, MA) can only be used for research purposes (Whyte et al,2000).

Both systems use their own database representing M. tuberculosis and many types of TDM. These methods have several disadvantages;

1. Databases may not be adequately representative of less common mycobacteria.
2. Identification requires the pure isolate for which it must be grown in culture and it is a time consuming process.
3. It cannot distinguish between species including MTBC members (Aricha et al, 2019; Buckwalte et al, 2016).

Also there are also publications reporting that mycobacterial species are correctly identified by both MALDI-TOF MS systems (Balada-Llasat et al, 2013; Mather et al, 2013). Akyar et al. showed that MALDITOF MS identified 94% of mycobacteria isolates and was successful in distinguishing MTBC from TDM isolates in their study evaluating MALDI-TOF MS (Bruker, Daltonics) (Akyar et al, 2018).

V.V. Moleculer line prob assay (LIPA): They are provide rapid identification of MTBC from culture and direct clinical samples. There are commercial LIPA tests from various companies. These have CE approval for MTBC detection in Europe but not FDA approval in the United States.

Speedoligo Mycobacteria (Vircell, Granada, Spain), INNO-LiPA Mycobacteria v2 (Fujirebio, Ghent, Belgium), GenoType MTBC (Hain

Lifescience, Nehren, Germany) kits can detect different numbers of TDM in addition to MTBC (Whyte et al, 2000). All three tests can be run from liquid and solid cultures and the first two can provide results in about four to six hours, while the third in three hours. LiPAs can quickly identify more than 90% of common mycobacteria. It is suggested that all results to be endorsed by phenotypic characteristics (reproduction rate, pigmentation, colony morphology, etc.) since they make a small number of misidentifications The sensitivity of the LPA test in the detection of M. tuberculosis was found to be 98.4% and the specificity as 66.0% in a study conducted by Aricha et al. (Brown-Elliott and Wallace, 2019).

V.VI. PCR-based sequencing: Nucleic acid amplification and sequencing are the gold standard for MTBC identification and TDM, and 16S rRNA is often used for identification (Whyte et al, 2000).

The primary leverage of its sequencing is that this concedes finding out numerous mycobacterial species including M. tuberculosis. Studies using 16S ribosomal RNA (rRNA) sequence-based identification methods for the identification of mycobacteria show that this technique is faster (weeks versus hours) and more accurate than conventional methods. However, the disadvantages are that it requires experienced personnel and includes protocols that require intense labor (Esen,2003; Turenne et al, 2001). The results of two different genotyping studies conducted in the same center in Turkey have been published. It was made from 470 M. tuberculosis strains, with the most dominant spoligotype being ST53, followed by ST41 (LAM7-TUR), ST50, ST284 and ST4 (Cavusoglu et al, 2017) in the first study. Second study performed on 171 extrapulmonary samples and it was reported that the major spoligotypes were T, LAM7-TUR (ST41) and H1 genotypes (Tasbakan et al, 2018).

VI. TESTS FOR SUSCEPTIBILITY TO ANTITUBERCULOSIS DRUGS

For MTBC, we can examine this under two main titles for MTBC as culture-based and molecular IDT.

I. Culture-based IDT
1. Proportion method
2. Liquid systems
3. Sensitized MycoTB MIC plate method

II. Molecular IDT

1. Probe-based methods; Xpert MTB/R test, GenoType MTBDRplus, GenoType MTBDRsl
2. Sequence-based methods.

VI.I.Culture-based IDT:

VI.I.I.Proportion method: It allows to determine the rate of resistant microorganisms at a certain drug concentration. The agar proportion method on solid media is the reference method for conventional growth-based IDT but it results in three to four weeks (Rodrigues et al, 2009). The consistency between the LJ proportion and the BACTEC 460 TB system for first-line drugs [streptomycin (S), isoniazid (H), R, ethambutol (E)] in MTBC isolates rates were found to be 85.3%, 92.4%, 95.4% and 92.4%, respectively, in a study comparing the LJ proportion method (Yurtsever et al, 2011).

VI.I.II. Liquid systems: BACTEC MGIT 960 (Becton Dickinson), VersaTREK Culture System II (Trek Diagnostic Systems, Cleveland, OH) systems have FDA approval for first generation antituberculosis IDT in MTBC .

Sümbül et al. found that 78.1% of MTBC isolates were susceptible to all first-line antituberculosis drugs and 21.9% were resistant to at least one drug in their study using the MGIT-960 SIRE kit from 278 Mycobacterium species samples. The MDR rate was 13.7% in resistant strains and 3% in all strains (Sumbul et al, 2020). Yazısız et al. found resistance to at least one of the first-line antituberculosis drugs in 26.7% of the isolates in their study of 1193 MTBC isolates with the MGIT 960 system. The MDR rate was found 7.0% in this study (Yazısız et al, 2019). H, R, E, S and pyrazinamide results were compared with those obtained with MGIT 960 in a study evaluating the reliability of the VersaT-REK system for M. tuberculosis IDT and no significant difference was found between the two methods (Espasa et al, 2012). E, H, R resistances were tested with both systems and the general categorical agreement was reported as 96.8% in the study evaluating the categorical agreement between MGIT 960 and VersaTREK (Martin et al, 2018).

VI.I.III. Sensitized MycoTB MIC plate method: The sensitized MycoTB plate is a structured microtitration plate for minimal inhibitory concentration (MIC) determination for first-line and second-line antituberculosis drugs containing lyophilized antibiotics. This method is used for study purposes and has not yet received FDA approval but there are studies reported to give reliable results for MTBC (Varıcı Balcı and Çavuşoglu, 2018; Ceyhan and Vezir, 2020).

VI.I.IV. Molecular IDT: Phenotypic IDTs remain the gold standard for determining drug resistance. It is recommended to use molecular-based IDT tests as a supplement. Determination of R and H resistance by molecular methods has high specificity and sensitivity since mutations tend to occur in predictable places. However, it is much more difficult to detect resistance to second-line drugs for which mutations are variable (Warshauer et al, 2019).

VI.V. Probe-based methods: R resistance (rpoB), GeneXpert MTB/R assay, GenoType MTBDRplus (Hain Lifescience, Nehren, Germany) H (katG and inhA) and R (rpoB) resistance,), fluoroquinolones (gyrA), GenoType MTBDRsl (Hain Lifescience, Nehren, Germany, aminoglycosides and cyclic peptides (rrs) and ethambutol (embB) detect mutations (Rodrigues et al; 2009). The GenoType MTBDRplus and GenoType MTBDRsl tests have been recommended by the WHO for rapid screening in the diagnosis of MDR TB (WHO, 2018). The sensitivity was reported as 62.50%, specificity 96.50% for GeneXpert, 90.0% sensitivity and 99.1% specificity for LPA in the study in which the MGIT IDT was taken as the gold standard in the detection of R resistance and the performances of GeneXpert and LPA were evaluated. It has been reported that LPA performs better than GeneXpert and is a good alternative to MGIT 960 in detecting resistance to R. IDT methods were compared using phenotypic and genotypic methods (GenoType MTBDRsl assays version 1.0 (Hain Lifescience GmbH, Nehren, Germany, MGIT 960, GenoType MTBDRplus version 1.0 (Hain Lifescience GmbH, Nehren, Germany),) and molecular patterns are given in a study conducted on 1329 MTBC isolates from Istanbul. The sensitivities of the genotypic methods for the detection of H, R, E, and MDR-TB were 77%, 84%, 65%, and 89%, and specificities were 99%, 98%, 67%, and 94%, respectively. MDR TB rate was found as 10.9% with the molecular method while it was 11.1% with the MGIT 960 system (Yazisiz, 2020). The results of a study comparing the MGIT 960 SIRE kit and the GenoType MTBDRsl test to determine susceptibility to second-line antituberculosis drugs in MDR-TB cases revealed that the GenoType MTBDRsl test is valuable in making early treatment decisions but the MGIT 960 SIRE kit should be used in addition to the routine evaluation of tuberculosis cases (Tekin et al, 2017).

VI.VI.Sequence-based methods: These tests have a sensitivity and specificity of over 85.0% was reported (except for E and moxifloxacin), and it was reported to be a promising approach in detecting many drug resistance in the study conducted with whole genome sequence analysis. (Chen et al, 2019). Concordance rates were found higher between whole genome analysis-based IDT and phenotypic DDT for first-line antituberculosis drugs, especially H and R in another study evaluating the concordance between phenotypic DBT and whole genome sequence analysis (Faksri et al, 2019).

RESULT

The success of the fight against tuberculosis depends on the reachability of applicable laboratory systems for correct and swift diagnosis of the malady. Traditional diagnostic methods still in use at the in tuberculosis laboratories. Nowadays use of new methods that allow earlier diagnosis and drug susceptibility test results is becoming widespread. The availability of diagnostic methods needs to be increased, especially in countries with limited resources.

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CHAPTER 4

SUICIDE BEHAVIOUR AMONG MEDICAL STUDENTS IN TURKEY

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Abstract

Objective: This study aims to determine suicidality and risk factors in medical students by means of evaluating the news in the media.

Methods: This retrospective study was performed using the Google search engine between 1-21 February 2022. Suicidal events of the medical students between January 2010-2022 were investigated. The Turkish "medical student, suicide" terms were used as keywords.

Results: In this study we have obtained suicide data of 29 medical students. Gender data of 27 students were reached of whom 9 were females and 18 were males. They had a mean age of 24.35±5.13 years (min.=19, max.=40). Fifteen students had suicide in clinical years (4-6th grade). The most common methods for suicide were jumping from heights (n=12), hanging (n=7), and firearms (n=4). The most frequent reasons for suicide were academic stress-anxiety (n=5) and psychological problems (n=4). The months when suicides most commonly took place were october (n=6) and november (n=4). It was determined that students committed suicide most frequently at home.

Conclusion: This study revealed that suicidality among medical students was more common in males. Suicides were committed at 20-22 year-olds and in the last 3 years of medical faculty (clinical years). The most frequent methods for suicide were jumping from heights and hanging. Academic stress- anxiety and psychological problems were at the forefront among identified suicide causes. The studies to determine suicide risk in medical students should be performed and preventive health policies against suicidality should be developed.

Keywords: Suicide, medical student, risk factors, anxiety, hanging

INTRODUCTION

Suicidal behaviour was defined as "the act of killing oneself deliberately" by the World Health Organization (WHO) (WHO, 2019a; WHO, 2019b). Suicide is a significant health problem with a day by day increasing importance in the world. According to the WHO, approximately 700,000 people die due to suicide annually and 77% of suicides occur in low- and middle-income countries (WHO, 2019a; WHO, 2019b). The fourth leading cause of death in 15-19 year-olds is suicides according to 2019 data (WHO, 2019a; WHO, 2019b). In the USA, the second leading cause of death in 10-34 year-old group was suicide causing loss of 47,500 lives in 2019 (CDC, 2019). In Turkey, suicide rate was 4.12/100.000 and 3,406 (2,626 men and 780 women) people died due to suicides in 2019 (TSI, 2019).

Recent studies reported that suicide risk was higher in medical students (Blacker, Lewis, Swintak, Bostwick, & Rackley, 2019; Rotenstein, Ramos, Torre, Segal, Peluso, Guille, & Mata, 2016). In a systematic review, the rates of suicide among medical students were found to be 3-5 times higher than the general population (Blacker, Lewis, Swintak, Bostwick, & Rackley, 2019). Furthermore, it was reported that medical students were 3 times more likely to die due to suicide compared to their peers (AAMCNews, 2022). Rotenstein et al. found that the prevalence of depressive symptoms was 27.2% and suicidal ideation was 11.1% in medical faculty trainees. Moreover, they reported that 7.4% had suicidal ideation in the last two weeks and 24.2% in the last year (Rotenstein, Ramos, Torre, Segal, Peluso, Guille, & Mata, 2016).

It was found that medical faculty students have high burden of risk factors for anxiety/depression/suicidality (Mata, Ramos, Kim, Guille, & Sen, 2016). The risk factors for suicide behaviour were depicted as academic stress, economic difficulties, familial problems, feeling of social isolation, exposure to trauma, substance and alcohol abuse, long working hours, malnutrition, psychiatric disorders, and accommodation problems in the literatüre (Arafat, & Mamun, 2019; Romo-Nava, Bobadilla-Espinosa, Tafoya, Guízar-Sánchez, Gutiérrez, Carriedo, & Heinze, 2019).

It was reported that medical students abstain from seeking psychiatric councelling despite having easy access for medical care (Tjia, Givens, & Shea, 2002). This condition causes students with suicide risk to be aside from psychiatric help.

In the literature, there are no studies regarding suicidality in medical students in Turkey. This study aimed to determine suicidality and risk factors in medical students by evaluating the news in the media.

Material and Methods

This retrospective study was performed between 10-21 February 2022 using the Google search engine. We investigated the medical student suicides between January 2010-2022. The Turkish terms “medical student, suicide” were used as keywords. All news in the media were categorized according to years and analyzed one by one. At the end of research, 859 news were obtained and conflicting and repetitive news were omitted. A total of 29 medical trainee suicides were noted. Twenty eight of these ended up with death while we could not reach prognostic data about one case requiring intensive care.

Statistical analysis: Statistical analyses were performed using the SPSS version 23.0. Mean, and standard deviation were determined.

Ethics committee approval was not obtained for this study since approval was not required according to ethical and legal regulations.

Results

This study obtained suicidal data of 29 students. The data included gender information of 27 trainees (female=9, male=18). The mean age was 24.35±5.13 years (min.=19, max.=40). Twenty three medical students’ knowledge about school grade had been announced in the news; 6 were 4th grade, 5 were 6th, and 4 were 5th grade students. Of the suicides, 16 were committed in the fall semester and 10 in the spring semester. Three students were having education in a private university, 24 were public university pupils, and we could not reach school data for 2 students. The accommodation data of 18 students were obtained. The most common place for residence were houses; 5 lived with their families, 3 lived with house mates, and 3 alone. The sociodemographic data were presented in Tables 1 and 2.

Table 1. Students sociodemographic and suicide data

No.	Date	Gender	Age	Grade	Accommodation	City	Venue	Method of suicide	Reason for suicide
1	July 2010	Male	30	NR*	Home- family	Kayseri	Home-family	Hanging	Problems in emotional affairs, Academic stress-anxiety
2	February 2011	Male	40	4	Home-alone	Istanbul	Hospital	Jumping from heights	Schizophrenia-Bipolar disorder, Academic stress-anxiety
3	January 2012	Male	NR	4	Home- family	Ankara	Home-family	Jumping from heights	NR
4	March 2013	Male	25	NR	NR	Istanbul	Shooting gallery	Firearms	NR
5	July 2013	Male	31	6	NR	Istanbul	Hospital	Jumping from heights	NR
6	November 2013	Female	27	6	Dormitory	Isparta	Domitory	Hanging	Financial distress
7	August 2014	Male	19	1	Home- family	Kırklareli	Home-family	Firearms	Sleep disorder
8	March 2015	Male	20	2	Dormitory	Aydın	Domitory	Jumping from heights	NR
9	May 2016	Male	25	6	Home-friends	Isparta	Home-friends	Hanging	NR
10	October 2016	Female	24	5	Home-friends	Izmir	Home-friends	Jumping from heights	Academic stress-anxiety
11	April 2016	Male	29	4	House	Izmir	House	Hanging	NR
12	April 2016	Female	25	6	Home- family	Izmir	Home-family	Hanging	Psychological problems
13	October 2017	Female	NR	NR	NR	Istanbul	NR	NR	NR
14	October 2017	Female	24	4	NR	Aydın	Faculty building	Jumping from heights	NR
15	December 2018	Male	19	1	NR	Istanbul	Shopping center	Jumping from heights	NR
16	November 2018	Female	21	4	Home- family	Malatya	Home-family	Hanging	NR
17	November 2019	Male	NR	2	NR	Aydın	Home-family	Jumping from heights	Panic attack
18	September 2019	Male	21	NR	House	Kastamonu	House	Firearms	NR
19	October 2019	Male	NR	3	House	Aydın	House	Drowning with gas	NR
20	January 2020	Female	NR	1	NR	Bolu	Home-family	Firearms	Psychological problems
21	October 2021	Female	NR	5	NR	Ankara	Training center	Jumping from heights	NR
22	March 2021	Male	NR	3	Home- alone	Istanbul	Home-alone	Hanging	NR
23	June 2021	Male	NR	6	House	Balıkesir	House	Intoxication	NR

24	February 2021	Male	23	4	NR	Çanakkale	Forest	NR	NR
25	October 2021	Male	NR	5	Home-alone	Diyarbakır	Home-alone	NR	NR
26	September 2021	Female	22	5	House	Denizli	Fabricking	Jumping from heights	Following a swindle
27	November 2021	NR*	20	NR	NR	Kayseri	Viaduct	Jumping from heights	Financial distress– Academic stress-anxiety
28**	April 2021	NR	22	NR	NR	Manisa	NR	Intoxication	NR
29	January 2022	Male	20	2	Home-friends	Elâzığ	Home-friends	Jumping from heights	Academic stress-anxiety, despair for fate of being a doctor,

* Not reported, ** We could not reach information whether the case is alive or not after the suicide attempt.

Table 2. Students sociodemographic and suicide data

Parameter	Variable	n
Gender	Male	18
	Female	9
Academic grade	1st grade	3
	2nd grade	3
	3rd grade	2
	4th grade	6
	5th grade	4
	6th grade	5
University	Public	24
	Private	3
Accommodation	House-family	5
	House-friends	3
	House-alone	3
	House-NR	5
	Dormitory	2
Month	October	6
	November	4
	January	3
	March	3
	April	3
Education period	1st semester (september-january)	16
	2nd semester (february-june)	10
Venue	House	16
	Dormitory	2
	Outside	9
Methods for suicide	Jumping from heights	12
	Hanging	7
	Firearms	4

	Intoxication	2
	Drowning	1
Reason for suicide	Academic stress-anxiety	5
	Psychological problems	4
	Economic challenges	2
	Emotional affairs or family problems	2

The data on suicide methods were reached for 27 students. The most common methods were jumping from heights (n=12), hanging (n=7), and firearms (n=4). Jumping from heights was the most frequent method for male and the female (male: 7, female: 4). As for reasons to commit suicide, 5 students had academic stress and anxiety, 4 had psychological problems (2 with psychiatric daignoses), and 2 had economic distress (Table 2). One student left a video record and 2 left letters behind before the suicide.

It was determined that students committed suicide most commonly in October (n=6) and November (n=4) (Table 2). Of the 29 students, we reached the data where suicide took place for 27 students. The most frequent venue was home of which 7 occurred in family houses (Table 2). The cities where suicides happened most commonly were İstanbul (n=6), Aydın (n=4), and İzmir (n=3) respectively (Table 1).

DISCUSSION

This study notes a total of 29 medical student suicides of which 28 resulted in death between 2010-2022. It was reported that 13 medical students in Bangladesh (Mamun, Misti, & Griffiths, 2020) between 2018-2019, 6 medical students in the USA (Cheng, Kumar, Nelson, Harris, & Coverdale, 2014) between 2006-2011, 16 students in India (Pruthi, Gupta, & Goel, 2015) between 2010-2014, and 6 students in Canada (Zivanovic, McMillan, Lovato, & Roston, 2018) between 2006-2016 committed suicides. It is obvious that suicide rates among medical faculty students are higher in underdeveloped and developing countries than developed ones. Indeed, 77% of suicides worldwide occur in low- and middle-income countries (WHO, 2019a). Our study reveals that the rate of medical student suicide is higher than that of the USA and Canada. This situation may have stem from the fact that Turkey is a developing country, differences in the curriculum of medical training, cultural structure of the societies, and demographic characteristics.

According to the WHO, suicide rate is 12.6 in males and 5.4 females per 100,000 in 2019 (WHO, 2019b). As for Turkey, the suicide rate (per 100,000) in 20-24 year-old males was 9.05, and 3.39 in female of the same age while the rate in 25-29 year-old males was 9.17, and 2.22 in the same-age females (TSI, 2019). In another study, total suicide rate was depicted to be 1.41 times higher in male doctors and 2.27 times higher in female doctors when compared to the general population (Schernhammer, & Colditz, 2004). In the current study, gender data was obtained for 27 students among whom 18 were males and 9 were females. Of the medical trainee suicides in the literature, 10 out of 16 cases from India (Pruthi, Gupta, & Goel, 2015) and 4 out of 6 cases in the USA (Cheng, Kumar, Nelson, Harris, & Coverdale, 2014) were males. In another study from the USA on medical students and doctors, suicide ideation was more frequent in men compared to women (Pospos, Tal, Iglewicz, Newton, Tai-Seale, Downs, & Zisook, 2019). Both in our study and the literature, the rate to commit suicide was higher in men. This may be due to inherently determined nature of men to commit a suicide or their roles in the society.

The mean age of students were 24.35 (min.=19, max.=40) years. In several studies carried out on medical faculty trainees, suicides occurred between the ages of 20-25 in Bangladesh (Mamun, Misti, & Griffiths, 2020), and between the ages of 22-29 (mean age:25.3 for male and 26.5 for female) in the USA (Cheng, Kumar, Nelson, Harris, & Coverdale, 2014). Our study established similar results with the literature.

We could obtain data about school grade for 23 cases. Fifteen students were in their clinical years (4-6th grade). Furthermore, 16 of the suicides occurred in fall semester while 10 happened in the spring semester. Mamun et al reported that 77% of medical students committed suicide in the clinical period and in the first semester of the academic year (Mamun, Misti, & Griffiths, 2020). Likewise, in the study by Zivanoviç et al., 5 out of 6 medical students committed suicide in the clinical period (Zivanovic, McMillan, Lovato, & Roston, 2018). In a study from the USA, all medical students' suicides between 2006-2011 took place in pre-clinical period (1-3 years) (Cheng, Kumar, Nelson, Harris, & Coverdale, 2014). Our results are compatible with those of Mamun and Zivanoviç. However, all the suicides in USA were in preclinical era. This conflicting result may have stem from the difference of difficulty degree of the terms of medical training across countries. The suicides most commonly occurred in the first months of the

first semester suggesting the possibility that academic stress, adaptation problems, and the distress of new academic period may be triggers.

In the current study, three students were form private universities, 24 were public university pupils and we could not reach the school data of two students. In Bangladesh, of the medical students committing suicide, 9 were from public universities and one was a private university pupil (Mamun, Misti, & Griffiths, 2020). These results of Turkey and Bangladesh demonstrating that suicides were more common in public universities may be explained by the fact that students are mostly educated at public medical schools in these countries.

In the present study, the most common methods for suicide were jumping from heights (n=12), hanging (n=7), and firearms (n=4). Jumping from heights was the most common method both for male and female students. In the study by Mamun et al from Bangladesh, 12 out of 13 medical students committed suicides by hanging and one by poisoning (Mamun, Misti, & Griffiths, 2020). In the USA between 2006-2011, 2 medical students committed suicide by firearms, 2 by hanging, and 1 by poisoning with overdose drugs (Cheng, Kumar, Nelson, Harris, & Coverdale, 2014).

Different suicidal methods were employed among medical faculty students in different countries. This situation may be due to the timeframe studies were conducted, demographic characteristics, economic and social development status of countries, religious values, and cultural factors. According to 2019 national data, 42.6% of 20-29 year-old individuals committed suicide by hanging, 34.8% by firearms, and 14.0% by jumping from heights in Turkey (TSI, 2019). The finding that medical students in Turkey more commonly preferred jumping from heights as a suicidal method than the general population is an issue to be investigated.

As for the suicidal reasons, 5 students had academic stress- anxiety, 4 had psychological problems (2 with psychiatric diagnoses), and 2 had financial distress. In studies evaluating medical students' suicides, the most prevalent causes for suicide were reported as low academic success and stress in India (Pruthi, Gupta, & Goel, 2015) and Bangladesh (Mamun, Misti, & Griffiths, 2020). Our results are in line with the literature. The major reason for suicide is academic failure and consequent stress in medical faculty students. Therefore, students with lower academic success should be assessed in terms of suicidal risk and preventive health policies should be constructed.

Additionally, another significant reason for suicide is psychological problems but the students' timidity to seek for psychiatric help obstructs to solve this problem (Tjia, Givens, & Shea, 2002). Psychiatry departments of medical schools should develop constructive approaches with this regard.

We have found that one student had left a video record and 2 had left letters prior to the suicide. In a study from the USA, 3 out of 6 medical students committing suicide left letters behind (Cheng, Kumar, Nelson, Harris, & Coverdale, 2014). It is important that medical students leave notes before suicides. These notes and data should be processed by the Ministry of Health and its stakeholders to identify the causes for suicidal behaviour and to investigate for solutions. Also, providing students with psychological councelling and guidance services by the medical schools is of great importance.

This study has revealed that suicides most commonly occcurred in October and November. In studies by Mamun et al. suicides most frequently took place in February and March (Mamun, Misti, & Griffiths, 2020) while Pruthi et al. reported January and March as the most common months (Pruthi, Gupta, & Goel, 2015). The suicides among medical students occur most frequently in autumn and winter. This situation may be explained by the effect of these months on mood and the stress arising due to first academic months.

The current study have shown that suicides were most commonly committed in the family houses. This is an important finding which may explain an increased change in private lives and more intense academic stress when staying with families that may have led to the suicidal behaviour.

This study merely dealed with data obtained from the media news which is an obstacle to reach suicide cases not published in the media. In addition, another drawback is missing or contradictory data of the news.

CONCLUSION

This study has revealed that male medical students committed self-suicide more commonly. The suicides took place between ages 20-22 and in the last three years (clinical stages) of the medical school. The suicides were most frequently performed at home. The most common methods for suicide were jumping from heights and hanging. Academic stress-anxiety and economic distress were the most prevalent causes among determinable ones. Having a history of psychiatric disease was another important factor. The

suicides most commonly occurred in the autumn. Consequently, studies to ascertain the risks for suicide in medical school students should be implemented and preventive health policies should be improved regarding suicides.

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CHAPTER 5

LOMBER SPINAL STENOZ

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INTRODUCTION

Pathoanatomy and Pathophysiology

Lumbar spinal stenosis (LSS) can be attributed to degenerative or congenital factors. The degenerative form becomes more prevalent as individuals age. Among people aged 60 to 69 years, approximately 50% exhibit mild stenosis, while almost 20% show more severe findings, even in asymptomatic subjects.(Kalichman et al., 2009) Degenerative LSS can be anatomically classified into three types:

- Central Stenosis: This type affects the central spinal canal along with the dural sac.
- Lateral Stenosis: Lateral stenosis occurs at the level of the facet joints, affecting the lateralrecesses.
- Foraminal Stenosis: Foraminal stenosis involves the narrowing of the neural foramina, throughwhich spinal nerve roots exit the spinal canal.

The prevalence of stenotic changes is highest at the L4-5 level, followed by the L3-4 and L5-S1 levels. These anatomical classifications help in understanding the location and extent of the narrowing in degenerative LSS. (Tomkins-Lane et al., 2014) In LSS, the narrowing of the spinal canal is typically caused by changes in the ligamentum flavum and marked hypertrophy of the facet joints, or a combination of both factors. In patients with LSS, the ligamentum flavum tends to be thicker compared to asymptomatic subjects. This thickening is believed to be a response to the degenerative changes and increased stress on the spine over time. As the ligamentum flavum thickens, it contributes to narrowing the space within the spinal canal, leading to compression of the spinal cord and/or nerve roots, which can result in various symptoms associated with lumbar spinal stenosis. (Abbas et al., 2010; Hansson et al., 2009) Indeed, in patients with LSS, the prevalence of facet joint osteoarthritis is notably higher compared to age-matched asymptomatic subjects, particularly at the L4-5 and L3-4 levels. (Abbas et al., 2011)

Congenital LSS occurs due to abnormal growth of the dorsal parts of the vertebrae during the prenatal period or early infancy. This growth disturbance can result in premature fusion of the posterior elements, leading to a universal narrowing of the lumbar spinal canal or segmental involvement of specific vertebrae, often affecting L3, L4, and L5. (Singh et al., 2005)

Typically, congenital LSS is characterized by short pedicles, which are the bony projections that connect the vertebral body to the facet joints. This shortening of pedicles reduces the anteroposterior (AP) diameter of the spinal canal. Additionally, some patients may have steeply inclined laminae and a narrow interpedicular distance, further shortening the transverse diameter of the spinal canal. (Kitab et al., 2014) As a result of these structural abnormalities, the cross- sectional area (CSA) of the spinal canal is significantly decreased in patients with congenital spinal stenosis when compared to control subjects. This reduction in CSA creates a mismatch between the size of the spinal canal and the volume of the neural elements. (Singh et al., 2005) Interestingly, among asymptomatic individuals, about 5% may exhibit mild signs of congenitally narrowed spinal canal, and 2.6% may have more severe findings, indicating that some people may have this anatomical variation without experiencing symptoms. (Kalichman et al., 2009) In patients with congenital LSS, symptoms typically arise at an earlier age and with less severe degenerative changes compared to patients with degenerative LSS. A congenitally narrowed spinal canal is also a distinctive feature of certain skeletal dysplasias, such as achondroplasia or diastrophic dysplasia, which are genetic conditions affecting bone development. These congenital factors play a crucial role in the development and presentation of LSS. (Jeong et al., 2006; Remes et al., 2001) The pathophysiology of symptomatic LSS is not fully elucidated, but various theories have been proposed to explain the underlying mechanisms leading to clinical symptoms. One well-known theory is the "double-crush" theory, popularized by Porter and Ward in the early 1990s. According to this theory, symptomatic patients with LSS usually experience compression of neural structures in at least two anatomical areas. This compression may occur at multiple levels or involve both central and foraminal locations of the spinal canal. The simultaneous compression at multiple sites can lead to more pronounced symptoms compared to isolated compression at a single level. (Porter & Ward, 1992) More recent research has provided additional insights into the specific clinical symptoms of LSS. According to some studies, the symptoms are thought to result from a combination of mechanical compression and disturbances in blood flow in the cauda equina or individual nerve roots. (Porter & Ward, 1992) The combination of mechanical compression and disturbances in blood flow likely contributes to the complex and varied clinical presentation of symptomatic LSS. However, the exact interplay of these factors and their relative contributions to the development of symptoms require further

investigation and research. (Kobayashi, 2014)

Natural History

The natural progression of LSS without specific treatment remains largely unknown. MRI studies have revealed evidence of significant LSS in around 20% of asymptomatic individuals aged over 60. (Porter & Ward, 1992) However, in a community-based MRI study, it was found that severe LSS was associated with symptoms, but less than 20% of patients with severe stenotic findings were actually symptomatic. (Ishimoto et al., 2013)

Clinical Characteristics of Lumbar Spinal Stenosis

The clinical course of LSS symptoms is characterized by a gradual onset and slow progression, with rapid or catastrophic progression being rare. Patients typically present with either intermittent neurogenic claudication or well-defined radicular pain. In large patient groups, those with single-level LSS, with or without degenerative spondylolisthesis, tend to exhibit a dermatomal pain pattern, while patients with multilevel stenosis commonly experience intermittent neurogenic claudication. (Park et al., 2010)

Intermittent neurogenic claudication is a typical symptom pattern in LSS. It includes pain, numbness, or tingling in the buttocks or lower extremities while walking or standing, with symptom relief observed when sitting or bending forward. Patients may also report paresthesias and chilliness in the lower extremities, as well as restless legs syndrome or leg cramps. The most common symptom complex associated with LSS is a lack of pain while sitting, improvement of symptoms when bending forward, and the presence of bilateral buttock or leg pain. Additionally, patients with LSS often experience severe lowback pain. (Sigmundsson et al., 2013)

Symptomatic LSS has a significant impact on patients' functional status and health-related quality of life. Patients with LSS generally exhibit lower health-related quality of life and worse health status compared to age-matched patients with chronic low back pain unrelated to LSS. The presence of LSS is associated with a greater burden on the individual's well-being and overall quality of life. (Battié et al., 2012)

Diagnosis of Lumbar Spinal Stenosis

There is currently no universally accepted diagnostic standard for LSS. The diagnosis of LSS is typically made based on the presence of characteristic symptoms in combination with radiographic evidence of

narrowing of the spinal canal. It is important to note that many individuals with radiographic evidence of spinal canal narrowing may remain asymptomatic, meaning they do not experience any symptoms related to the stenosis. Therefore, a careful correlation between the clinical symptoms reported by the patient and the imaging findings is crucial for making sound treatment decisions.

According to a systematic review, the most sensitive symptom for the diagnosis of LSS is radicular pain that worsens when standing. This symptom is particularly indicative of LSS and can be a key factor in diagnosing the condition. Additionally, certain clinical signs are informative in identifying symptomatic LSS. These include the presence of bilateral buttock or leg pain, the absence of pain when sitting, and an improvement of symptoms when bending forward. These signs can be valuable in supporting the diagnosis of LSS. (De Schepper et al., 2013)

Overall, a combination of the characteristic symptoms and the presence of radiographic evidence of spinal canal narrowing is essential for a reliable diagnosis of LSS. Clinical examination findings, while less useful on their own, can still contribute to the overall assessment of the patient's condition and help guide appropriate management and treatment decisions. (Atlas et al., 1996)

Electrodiagnostic testing is not routinely necessary for diagnosing LSS, but it can be beneficial in patients with atypical symptoms or when there's poor correlation between symptoms and imaging findings. A complete electrodiagnostic examination may be required to differentiate LSS symptoms from those of peripheral neuropathy or neuromuscular diseases. Imaging studies, particularly MRI, are the preferred tests for confirming the clinical diagnosis in patients with suggestive symptoms of LSS. Plain radiographs, including functional flexion-extension views, are not helpful in quantifying the severity of the symptoms. (Drury et al., 2009)

There are no universally accepted radiologic criteria for LSS. However, various measurements have been used to assess spinal canal dimensions. The anteroposterior (AP) diameter of the lumbar spinal canal on plain radiographs and the cross-sectional area (CSA) of the bony spinal canal on transaxial CT images have been used for quantitative evaluations. Absolute congenital stenosis was defined based on the anteroposterior (AP) diameter of the spinal canal, with a measurement of less than 10 mm. Relative congenital

stenosis, on the other hand, was defined as an AP diameter ranging between 10 and 12 mm. These measurements serve as criteria for assessing the severity of congenital narrowing of the spinal canal. (Verbiest, 1975)

Additionally, the CSA of the dural sac was introduced to better describe the morphology of spinal stenosis. Generally accepted borderline values for the dural sac CSA in absolute LSS (<75 mm^2) and relative LSS (<100 mm^2) were established. (Schönström & Hansson, 1988) However, using the smallest CSA of the dural sac for LSS determination may lead to both overdiagnosis and underdiagnosis. Overdiagnosis may lead to unnecessary treatments, interventions, or surgeries that might not provide any significant benefit to the patient. In some cases, imaging findings may indicate anatomical changes associated with spinal stenosis, but these changes may not be the primary cause of the patient's symptoms. Other factors, such as age-related degenerative changes or conditions unrelated to spinal stenosis, could be responsible for the patient's symptoms.

In clinical practice, the degree of LSS visible on MRI is often described qualitatively as mild, moderate, or severe based on subjective judgment.(figure1) Clinical decisions and treatment planning should not solely rely on this grading system but should take into account the patient's symptoms, physical examination, and overall clinical presentation to guide appropriate management for LSS. (Schizas et al., 2010)

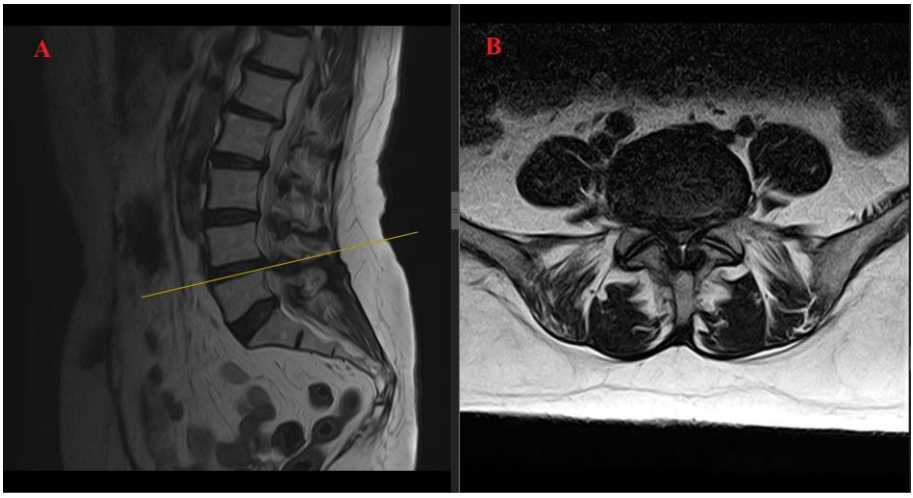

Figure 1: Images of lumbar spinal stenosis. A, Sagittal T2-weighted magnetic resonance image(MRI). B, Axial T2-weighted MRI

Differential Diagnosis

Peripheral arterial disease (PAD) and hip joint osteoarthritis can produce symptoms similar to those ofLSS and may coexist with LSS in some cases. Concomitant PAD in patients with LSS is more common among older individuals, those with diabetes, and those with aortic calcifications. (Han et al., 2013)

Differential diagnosis between these conditions should primarily rely on the patient's medical history rather than relying solely on physical examination findings. Symptoms localized above the knees, worsened by standing, and relieved by sitting are indicative of neurogenic claudication, which is commonly associated with LSS. On the other hand, symptoms below the knees that improve when standing still suggest a vascular cause, which might be related to peripheral arterial disease. (Haig et al., 2013; Nadeau et al., 2013)

In patients experiencing symptoms caused by both hip joint osteoarthritis and LSS, the recommended approach is to prioritize total hip arthroplasty (THA) as the first treatment option. This is because in caseswhere the hip joint has osteoarthritis with associated flexion contracture, it can lead to significant lumbar lordosis as the body attempts to maintain overall balance. This increased lumbar lordosis can further exacerbate the symptoms of LSS. (McNamara et al., 1993)

Treatment

The decision to pursue either conservative or operative treatment for symptomatic LSS is primarily dependent on the severity of the symptoms, rather than the degree of radiographic findings. The main goal of treatment is to alleviate pain, enhance function, and improve mobility. (Miyamoto et al., 2008) Generally, conservative treatment is considered the initial approach, and it may still provide benefits for patients with severe symptoms. Patients who opt for operative treatment typically present with more severe symptoms, reduced functional ability, and more pronounced imaging findings compared to those who choose conservative measures. However, it's important to note that, currently, there is no evidence supporting the superiority of any treatment method over the natural progression of LSS. Unsatisfactory outcomes have been reported in approximately 35% to 40% of patients treated operatively and in around 50% to 60% of patients treated conservatively. (SJ, 2000)

- **Conservative treatment**

Conservative treatment options for LSS have limited supporting evidence regarding their efficacy. Common approaches include using nonsteroidal anti-inflammatory drugs (NSAIDs) to manage pain, educating patients about their condition, implementing muscle strengthening and endurance exercises, and employing various physical therapy techniques. In long-term follow-up studies, patients treated conservatively have reported either stable or moderately improved symptoms. For example, in the Maine Lumbar Spine Study, 44% of conservatively treated patients experienced an improvement in their predominant pain after a 10-year period. (Atlas et al., 2005) It is worth noting that no catastrophic events, such as cauda equina syndrome, have been reported with conservative treatment. (Weinstein et al., 2008)

Indeed, the current evidence regarding the efficacy of oral medications in treating LSS is of very low or low quality. (Ammendolia et al., 2012; Ammendolia et al., 2014) Specifically, the effectiveness of calcitonin as a treatment for LSS has been found to blacking significant improvement in walking ability when compared to placebo or acetaminophen,regardless of the route of administration. (Ammendolia et al., 2012; Coronado-Zarco et al., 2009; Podichetty et al., 2011)

The role of physical therapy in the treatment of LSS remains uncertain, as there is no clear evidence indicating that any specific physical therapy intervention leads to improved walking ability. (Macedo et al., 2013) Various physical therapy modalities have not shown superiority for LSS symptoms, and adding different modalities to exercise does not appear to increase its effectiveness. (Macedo et al., 2013) Exercise, as part of physical therapy, has shown short-term benefits in reducing pain and improving function. However, there is no evidence supporting the preference of one exercise program over others for LSS treatment. (Ammendolia et al., 2012)

- ***Operative Treatment***

In 1954, Verbiest elucidated the connection between LSS and cauda equina compression, detailing successful management through neural structure decompression. (Verbiest, 1954) Since his groundbreaking work, conventional treatment for LSS symptoms has involved extensive laminectomy and undercutting of facet joints and neural foramina. However, suboptimal outcomes have been linked to iatrogenic spinal instability

resulting from the removal of posterior stabilizing elements. Advances in spinal imaging have facilitated precise identification of LSS's anatomical extent, leading to more targeted surgical approaches like laminotomy and segmental interlaminar decompression. Biomechanical studies underscore the significance of the posterior tension band (consisting of the spinous process and the supraspinous and interspinous ligaments) in maintaining spinal stability. (Bresnahan et al., 2009)

Starting from the mid-1990s, minimally invasive techniques have been introduced to preserve dorsal midline structures. While preserving the stabilizing paravertebral muscles, midline structures, and facet joints may be crucial for effective LSS management, ensuring adequate decompression of neural elements remains the primary objective. (Poletti, 1995) Post-decompression, thedural sac gradually expands, a process continuing for up to a year after surgery, with more significant increases seen in the later postoperative phase compared to immediately after the operation.

As of now, no conclusive evidence guides the selection of a particular surgical procedure for individual patients. The combination of spinal fusion with decompression does not lead to increased patient satisfaction, regardless of the presence of spondylolisthesis. Consequently, making surgical decisions in any clinical scenario necessitates considerable subjective judgmentbased on individual patient characteristics. (Försth et al., 2016)

1. Surgical Technique: Interlaminar Decompression

To achieve successful decompressive surgery for LSS, careful preoperative review of spinal imaging is crucial to identify the structures compressing neural elements and the extent of stenosis. Patient positioning aims to decompress the abdomen to prevent excessive epidural bleeding during spinal canal exploration. Specific operating tables or the traditional knee-chest position can be used for this purpose. Fluoroscopy is utilized to localize and mark the target level before making the incision. Special attention is given to structural anomalies, such as transitional vertebrae, through meticulous analysis of spinal imaging and fluoroscopy.

The surgery involves making a midline incision over each level to be decompressed, followed by elevating paraspinal muscles to the level of facet joints. The supraspinous and interspinous ligaments are removed, along with portions of the upper and lower spinous processes and the ligamentum flavum. In cases of significant facet joint hypertrophy, resection of the

articular processes may be necessary for lateral decompression. Preservation of the pars interarticularis is vital to prevent iatrogenic fractures. (Hasegawa et al., 2013)

A blunt dissector or round-tipped nerve hook confirms the extent of decompression. Adequate hemostasis is ensured before wound closure. The use of closed suction drainage after decompression is at the surgeon's discretion, as studies have not shown significant differences in outcomes. (Brown & Brookfield, 2004; Payne et al., 1996) For multilevel stenosis, interlaminar decompression can be performed segmentally to each stenotic level, or bilateral laminectomy can be considered as an alternative approach. Overall, meticulous planning, precise execution, and individualized techniques are essential for successful decompressive surgery in LSS cases.

2. Surgical Technique: Bilateral Decompression through Bilateral or UnilateralLaminotomy

In the bilateral laminotomy technique, the surgeon preserves the spinous process, supraspinous, and interspinous ligaments. The paraspinal muscles are elevated bilaterally, and each side is decompressed separately under microscopy. Starting from one side, both the proximal and distal laminae are resected, detaching the attachments of the ligamentum flavum.The ligament is then resected carefully, protecting the neural elements. If necessary, facet joint and neural foramen undercutting is performed to finalize the decompression. In cases of bilateral LSS, the procedure is repeated for the contralateral side.

A modification of this technique is bilateral decompression using a unilateral laminotomy approach. Here, the initial side is decompressed similarly to the bilateral laminotomy technique, with retraction of the paraspinal muscles from this side only, preserving the posterior anatomy of the contralateral side. The contralateral side is visualized by angling the microscope and tilting the operating table. After exposure, the contralateral ligamentum flavum and facet joint are resected until the contralateral pedicle and lateral border of the dural sac are identified.

Microendoscopic decompression, another modification, combines microsurgical techniques with a tubular retractor system and endoscopy. This method minimizes damage to the ipsilateral paraspinal muscles. When using the unilateral technique, an approach from the more symptomatic side is recommended. For bilateral and similar symptoms, approaching from the left

side may be more convenient for right-handed surgeons. Successive levels can be decompressed through the same approach, but further successive levels may require an approach from the opposite side. Facet joint resection tends to be greater on the ipsilateral side, especially at upper lumbar levels. Postoperative imaging studies show greater preservation of facet joints on the contralateral side. (Dohzono et al., 2013; Matsumura et al., 2010)

The microendoscopic technique has its challenges, such as limited visualization through the retractor and a steep learning curve for instrument maneuvering. An intraoperative switch to a standard procedure is recommended in case of problems during minimally invasive decompression procedures, especially during the early stages of the learning curve. (Ang et al., 2015)

Surgical Complications

Perioperative complications occur in 6% to 15% of patients undergoing decompressive surgery, with postoperative complications affecting 8.2% to 20% of patients. The overall mortality related to surgery ranges from 0.3% to 0.5%. (Kovacs et al., 2014; Weinstein et al., 2008) Major medical complications are seen in 3.1% of patients, and this incidence increases with greater comorbidity. Age, poor American Society of Anesthesiologists (ASA) status, and intraoperative blood loss also contribute to a higher risk of general complications. (Deyo et al., 2010) The rate of perioperative surgical complications does not show a significant increase with age.

Fusion surgery has variable effects on the complication rate; complex fusion procedures increase the risk of major medical complications and postoperative mortality. However, the overall complication rate and the rate of new postoperative neurological deficits are not significantly affected by concomitant fusion. Multilevel decompression procedures do not lead to an increased occurrence of complications, and minimally invasive decompression techniques show similar rates of surgical complications compared to open procedures. (Sobottke et al., 2012)

The incidence of incidental dural tears during decompressive surgery ranges from 0% to 22% for conventional open decompression and 0% to 15% for various minimally invasive techniques. (Ang et al., 2015; Thomé et al., 2005; Weinstein et al., 2009) Certain factors, such as older age, female sex, smoking, hypertension, and diabetes, increase the risk of dural tears. However, incidental dural tears do not lead to an increased incidence of neural

damage or postoperative infection, and they do not affect long- term clinical results in terms of pain, function, and health-related quality of life. Spinal epidural hematoma is a relatively uncommon complication, with reported incidences varying between 0% and 5% for lumbar decompressive surgery. (Jones et al., 2014; Thomé et al., 2005; Yoshimoto et al., 2014) Multilevel surgery does not increase the risk of symptomatic postoperative epidural hematoma. (Modi et al., 2011) Early diagnosis and immediate surgical decompression are crucial for a successful outcome if spinal epidural hematoma is suspected. Secondary formation of a synovial facet cyst is seen in 5% to 18% of patients within the first postoperative year and may lead to recurrent radicular symptoms. (Kato et al., 2013; Walcott & Coumans, 2012) Preoperative risk factors for facet cyst formation include instability, asymmetrical disk degeneration, and sagittal imbalance. The incidence of reoperation for recurrent stenosis or degenerative instability increases with follow-up, with rates ranging from 3% to 23% depending on the duration of follow-up. (Deyo et al., 2011)

Reoperation can result in significant improvement in pain and function, although not to the same extent as primary surgery. The decision for revision surgery should be based on the patient's symptoms, and waiting for postoperative MRI may delay necessary revision surgery.

Postoperative Rehabilitation

The available evidence suggests that postoperative rehabilitation for LSS patients lacks a universally agreed-upon standard approach. (Mannion et al., 2007) While supervised exercise programs and physical therapy did not show significant benefits in surgical outcomes, the meta-analysis suggests that active postoperative rehabilitation might have some advantages in terms of function and back and leg pain. Nevertheless, further research is needed to establish a more definitive and effective postoperative treatment program for LSS patients. (McGregor et al., 2014)

Surgical Outcome

Decompressive surgery generally leads to a considerable reduction in pain and disability for patients with LSS. However, it's important to note that the quality of life of patients with LSS after surgery may not reach the same level as an age-matched population without the condition. (Jansson et al., 2009) The greatest benefit from surgery is typically observed within 3 to 6 months afterthe procedure, followed by a relatively stable situation in terms of

most outcome parameters. However, poor outcomes have been reported in 15% to 40% of patients, irrespective of the surgical technique used. Severe low back pain or continued difficulty in walking are significant factors associated with a less favorable outcome. (Yamashita et al., 2003) In the Maine Lumbar Spine Study, two groups of patients with LSS were followed for 8 to 10 years. Those who initially underwent surgical treatment reported better outcomes up to 4 years later compared to those who received conservative treatment. However, at the long-term follow-up, both groups showed similar overall satisfaction with treatment, though surgically treated patients reported greater improvement in leg pain. (Schönström & Hansson, 1988; SJ, 2000)

In two randomized controlled trials, surgical treatment was compared to conservative measures for patients with LSS. Up to 2 years later, patients who underwent surgery experienced less leg pain compared to those who received conservative treatment. (Malmivaara et al., 2007) However, at the 6-year follow-up, no significant difference was found between the groups in terms of leg pain or walking ability. Nonetheless, surgical treatment showed superior functional status, as measuredby the Oswestry Disability Index, even at the 6-year mark. In the Spine Patient Outcomes Research Trial (SPORT), patients with LSS were randomized to undergo either standard decompressive laminectomy or "usual care." The results favored surgery for all outcomes during the 4-year follow-up period. Clinically significant improvement in disability was achieved by a higher percentage of surgically treated patients compared to conservatively treated patients. (Weinstein et al., 2008)

There is a debate regarding the role of concomitant fusion surgery for patients with LSS and significant low back pain. Some advocate for fusion surgery, but convincing evidence of back pain improvement is lacking. Notably, significant improvement in back pain has been reported after decompression without fusion, possibly due to improved lumbar posture and facet joint denervation resulting from surgical trauma. Based on updated guidelines, concurrent fusion is not routinely recommended in the absence of deformity or instability since there is no evidence of improved outcomes. Several randomized controlled trials have compared minimally invasive techniques with standard decompression. In one study, bilateral laminotomy, bilateral decompression via unilateral laminotomy, and standard laminectomy were compared, with bilateral laminotomy showing superior patient satisfaction. Other trials comparing different minimally invasive techniques or

conventional decompression did not reveal significant differences in functional outcomes, back pain, leg pain, or neurogenic claudication at the follow-up.

Prospective observational studies have reported positive results with different minimally invasive decompression procedures, but comparative studies have not consistently shown the superiority of minimally invasive techniques over traditional decompression regarding pain improvement, disability, quality of life, or walking ability. However, minimally invasive techniques did demonstrate significantly shorter postoperative hospital stays.

In conclusion, decompressive surgery remains favored over conservative treatment for pain relief, disability improvement, and quality of life enhancement. However, the benefits decrease with time, and the role of concomitant fusion surgery is still a subject of debate. Minimally invasive techniques offer the advantage of shorter hospital stays but do not consistently show superiority over traditional decompression in terms of pain and functional outcomes.

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CHAPTER 6

ACUTE EPIDURAL HEMATOMAS

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INTRODUCTION

Acute epidural hematomas are one of the common complications after head trauma. They constitute 30% of all intracranial hemorrhages. Acute epidural hematomas occur as a result of blood accumulation between the dura mater and the skull bone. They are observed in less than 2% of patients who have suffered cranio-cerebral trauma (Becter,2011).

The classical concept that these types of bleeding are arterial in origin has changed in later years, and it has been observed that epidural hematomas that occur in the late stages following head trauma are of venous origin (Michael,1986).

Epidural hematomas are often seen in the temporal and frontal regions but can also occur in other locations (Gökalp, 1983). In a study by Bellotti and colleagues, it was stated that 4-12% of epidural hematomas were posterior fossa epidural hematomas (Bellotti, 1987. Unlike convexity epidural hematomas, midline epidural hematomas are seen in the supra tentorial region in relation to the sinus sagitalis superior. The incidence of midline epidural hematomas is about 1-8 % of all epidurahematomas.(GuhaA,1989; Wylen EL,1998)

Epidural hematomas develop due to the tearing of dural venous sinuses, diploic veins, dural arteries, or veins along the edges of fractured cranial bones. The most frequently traumatized vessel is the arteria meningea media (Becter, Miller, Young, 2011; Gökalp, 1983; Ergüngör, 1988; William, 1995).

They are often seen in conjunction with linear fractures of the skull. However, epidural hematomas can also occur in cases where there are no linear skull fractures (Jimmy, 1990).

Epidural hematomas can occur in children without a skull fracture. (Evans, 1984; Ergüngör, 1983).

Cerebral contusion, acute subdural hematoma, traumatic subarachnoid hemorrhage, and intracerebral hematoma may occur with epidural hematomas (Ergüngör, 1988).

Clinical symptoms and signs of epidural hematomas manifest after trauma, and they appear in approximately one-third of patients within 2-7 days following the trauma (Sakai, 1988).

In cases of epidural hematomas, an increasing headache and a tendency to fall asleep occur after a variable latent period. This clinical condition is referred to as a lucid interval. Identifying the presence of a lucid interval in the patient's history who has experienced head trauma is a crucial finding in the diagnosis of epidural hematomas. Common clinical symptoms include impaired consciousness and coma, hemiparesis, and unilateral pupil dilation. The emergence of a loss of consciousness after a lucid interval should raise suspicion of an epidural hematoma (Gökalp, 1983; Ergüngör, 1988; William, 1995).

Subsequently, symptoms of medullary compression such as vomiting, irregular respiration, bradycardia, strabismus, decerebrate and decorticate postures develop (Ergüngör, 1988; Gökalp, 1983).

Linear fractures crossing the temporal fossa are often seen in direct skull X-rays and computerized brain tomography (CT). Linear fractures can be observed in all regions of the skull.

In CT examinations, epidural hematomas appear as hyperdense areas and have a biconvex shape.

The biconvex structure is adjacent to the inner table of the skull.

In Magnetic Resonance Imaging (MRI) examinations, acute epidural hematomas exhibit images related to fresh blood clots with long T1 and short T2 relaxation times (Elster, 1989). Subacute and other degradation products show images with a short T1 signal (Elster, 1989).

Epidural hematomas can occur at any age. A study by Balevi et al. reported that they are frequently observed in males and in the young and adult age groups (Balevi, 1992). They are less common in children in the first two age groups and in individuals over 60 years of age (Becter, 2011). D'Andrea and colleagues reported that pediatric epidural hematomas constitute 2% of all epidural hematomas (D'Andrea,2022; Khaled Chowdhury, 2012).

Wasfie and colleagues reported in their study that acute traumatic epidural hematomas are infrequently observed in the elderly (Wasfie, Shapiro, 2022). Balevi et al. reported in their study that the frequency of epidural hematomas in patients over 50 years of age is 1.86% (Balevi, 1992).

The reason why epidural hematomas are rare in people over the age of 60 is that the dura mater adheres to the inner surface of the skull in later ages. (Becter, 2011).

Linear skull fractures are present in 75-90% of epidural hematoma cases (Balevi,1992; Becter, 2011; Gökalp, 1983; William, 1995). Jimmy and colleagues reported that it is not always necessary for a skull fracture that could cause an epidural hematoma to be present (Jimmy, 1990). In a study by Balevi and colleagues, they reported that in 7.06% of cases, no radiological or intraoperative evidence of a linear fracture that could cause an epidural hematoma was observed. Especially in children, the absence of a linear fracture that could cause an epidural hematoma is more common (D'Andrea,2022).

William et al.reported that in temporal epidural hematomas, the arteria meningea media is often injured (William,1995).

Cerebral contusions and intracerebral hematomas can be observed alongside epidural hematomas (William, 1995).

Wasfie and colleagues reported in their study that acute traumatic epidural hematomas are infrequently observed in the elderly (Wasfie, 2022). Balevi and colleagues reported in their study that the frequency of epidural hematomas in patients over 50 years of age is 1.86% (Balevi, 1992). The reason for the infrequent occurrence in patients over 60 years of age is the firm adherence of the dura mater to the inner table of the skull, which tends to increase with advancing age (Becter, 2011).

Linear skull fractures are present in 75-90% of epidural hematoma cases (Balevi, 1992; Becter, 2011; Gökalp, 1983; William, Cormick, 1995). Jimmy and colleagues reported that it is not always necessary for a skull fracture that could cause an epidural hematoma to be present (Jimmy, 1990). In a study by Balevi and colleagues, they reported that in 7.06% of cases, no radiological or intraoperative evidence of a linear fracture that could cause an epidural hematoma was observed. Especially in children, the absence of a linear fracture that could cause an epidural hematoma is more common (D'Andrea, 2022). William and colleagues reported that in temporal epidural hematomas, the arteria meningea media is often injured (William, 1995).

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Minimal midline shifting hematomas and superficial epidural hematomas that do not cause pressure on the brain and minimal are typically treated medically with close observation (Rosenthal,2017).

Chronic epidural hematomas cause headache and various neurological symptoms. (Lim,2021). Traumatic chronic epidural hematomas can occur several days or weeks after a head injury (Bonilha ,2003; Oliveira Sillero ,2008; Iwakuma ,1973; Kaye,1985; Kim do ,2014).The incidence of chronic epidural hematomas is unknown. Iwakuma et al ,reported that it accounts for 9–32% of all epidural hematomas ((Iwakuma, 1973).

Supratentorial midline hematomas can be difficult to diagnose and treat. (Guha,1989; Wylen ,1998). When surgical treatment of supratentorial midline hematoma is necessary, two separate craniotomies should be performed. Güçlü,2022).

Surgical indications for clearance of epidural hematoma by craniotomy are as follows (Wang,2009): (1) hematoma >40 mL and located at the supratentorial region or hematoma >10 mL and located at the infratentorial region; (2) obvious midline structure shift (>1 cm) and ventricle or cisterna pressure; (3) intracranial pressure >2.7 kPa (270 mm H20) and progressively increasing; (4) consciousness dysfunction gradually worsening, even if bleeding amount does not meet the surgical indication criteria.

Surgical Treatment: After radiological localization of the hematoma, a craniotomy is performed on the skull, and the hematoma is aspirated. If there are bleeding dural vessels, they are controlled using bipolar electrocautery or sponges. Bone bleeding is stopped using materials like bone wax. To prevent blood accumulatıon ın the epıdural dıstance,,the dura mater is firmly attached to the pericranium. A drain is placed during the closing phase of the operation.

In a study by Balevi,,the mortality rate was reported as 24.71%. According to a study by Ramiro et al. , the mortality rate varies between 25% and 43% (Ramiro, 1988; Balevi, 1992). Mortality rates in children are lower (10% to 15%), but they rapidly increase in individuals over 40 years of age (35% to 50%) (William, Cormick, 1995).

Acute epidural hematomas have low mortality and morbidity rates if they are operated during the lucid interval period.

CONCLUSION

Early diagnosis and treatment are essential for acute epidural hematomas resulting from head trauma. It should not be forgotten that epidural hematomas can also occur in cases where there is no linear fracture in the skull.

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CHAPTER 7

THE EFFECT OF CHILDHOOD EPILEPSY ON THE FAMILY

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INTRODUCTION

Epilepsy is a common neurological disease in society. Central nervous system infections may occur due to structural, metabolic, immune and genetic diseases or may occur without an apparent cause (Canpolat et.al.,2014; Serdaroğlu et.al., 2004). The emergence of transient findings due to abnormal neuronal activity in the brain is called epileptic seizure (Fisher et.al., 2014). The quality of life in children with epilepsy may vary depending on different factors according to their age. It is important for parents and children to know that epilepsy in children can make life difficult.

The unpredictability of seizures causes constant anxiety for the child himself as well as for the family. In addition to seizure periods, there are other social, psychological, behavioral, educational and cultural factors that affect the lives of children with epilepsy, their families and close social circles. These factors differ from one patient to another, but have a significant impact on the quality of daily life of every child with epilepsy. Many children with epilepsy experience problems due to the side effects of anti-epileptic drugs, where they do not have adequate education and higher education is lower than the population (Mollaoğlu, 2015). In addition to the child with epilepsy, the quality of life also changes for other family members, especially healthy siblings.

Studies on the evaluation of health-related quality of life in children with epilepsy are very limited. The diagnosis of chronic disease can affect not only the individual psychology and emotions of family members, but also their relationships with other family members. For this reason, it is extremely important to evaluate the quality of life of children with epilepsy, as well as the quality of life of their healthy siblings.

Epilepsy

Epilepsy is a common neurological disease in society. Epilepsy is one of the most frequently diagnosed neurological diseases in childhood with an average prevalence of 0.5-1%. This rate is higher in the first year of life and gradually decreases after the age of 1 (Canpolat et.al.,2014**).** In the prevalence studies conducted in our country, its frequency was found to be 8-13.5/1,000 individuals (Canpolat et.al.,2014; Serdaroğlu et.al., 2004). The importance of epilepsies in neurological diseases is not only due to its frequent occurrence. The fact that epileptic manifestations have a very rich spectrum of clinical manifestations, from seizures observed in newborns to seizures in adults, and

the neurophysiological features of the event constitute the main and interesting aspect of this field (Mollaoğlu, 2012). The International League Against Epilepsy (ILAE) defined epileptic seizure and epilepsy disease separately (Canpolat et.al.,2014; Serdaroğlu et.al., 2004).

For the diagnosis of epilepsy, one of the following three items must be met.

- At least two unprovoked (or reflex) seizures occurring >24 hours apart;
- An unprovoked (or reflex) seizure and a high risk of seizure recurrence over the next 10 years (at least 60%);
- Defined as patients diagnosed with a specific epilepsy syndrome after the first seizure (Fisher et.al., 2014).

Epilepsy Classification

Classification of epileptic seizures was made by ILAE in 1981. He made the classification of epilepsies and epileptic syndromes in 1989. This classification has been widely used all over the world for a long time (Scheffer et.al., 2017; Tahrp, 1987).

Classification is always a dynamic process that allows for new research and a better understanding of the disease, and can thus lead to a significant advance in patient care (Fisher et.al., 2017; Scheffer et.al., 2017). Finally, a three-stage approach is recommended in the classification of epilepsy made by ILAE in 2017; classification of seizure type, epilepsy type and finally epilepsy syndrome. From the first epileptic attacks onset, evaluation in terms of etiology has been suggested at each step of the epilepsy classification. Etiologies are basically divided into six groups: Structural, genetic, infectious, metabolic, immunological, and unknown group (Wirrell et.al., 2022; Scheffer et.al., 2017; Fisher et.al., 2014).

Childhood Epilepsy

Epilepsy is the most common neurological disorder in childhood and adolescence (Lee, 2002; Jacoby et.al.,1996). The prevalence of childhood epilepsy is approximately 0.5%. as much. Approximately 50% of epilepsies are at the age of 5 years and 75% are at the age of 20. (Baum et.al.,2007; Rodenburg et.al., 2005). Serdaroğlu et al. (Serdaroğlu et.al., 2004) 0-16 reported the prevalence of epilepsy in Turkish children between the ages of 3,8%. Of these epileptic patients, 55.2% were generalized, 39% partial, and

5.8%. grouped as undefined. Epilepsy affects 3-5% of people. affects some developmental periods during their lifetime. **(**Baum et.al.,2007**)** All three epilepsy Two of the cases begin within the first 20 years of development and this cause undesirable consequences in the development of the child and in the life of the family. It is possible.

The Effect of Epilepsy in Children

In children, epilepsy is seen with power disorders, behavioral changes, psychiatric disorders, seizure-related accidents, side effects of drugs and increases in physical diseases. It is neurobiological, affecting the central nervous system. It causes cognitive, psychological and social disorders. It affects the attention function more in the younger age group than the later age group, and in this way it can affect the mental activities (Ovsonkova et.al., 2014; Augiar et.al., 2007).

In cases where adequate treatment is not received, epileptic seizures, which occur due to various reasons, due to the unknown location and time in children, cause mental retardation and psychological disorders in children, the perception of controlling social life to a large extent, restrict daily activities in social life, and also cause low self-confidence and stigmatization in children. It has a negative impact on learning in school-aged children (Fazlıoğlu et.al., 2010; Johnston, 2008).

Effects of Epilepsy on the Family

Epilepsy is successfully controlled by drug therapy in 70-80% of patients. role of parents of children with epilepsy a sense of loss of control paired with social labeling It increases periodic family stress and affects family adjustment (Mu, 2005). Numerous Parents experience sadness when their child is diagnosed with epilepsy. The typical first response of parents is denial, shock, devastation, disappointment, grief, and depression is the rating. For the family, witnessing their child's seizure (especially tonic-clonic seizure) is one of the most worrisome experiences. Given that psychosocial development is influenced by many factors, from individual and family factors to community and wider factors, how the child and family members respond to the child's illness depends on a number of factors, from personal factors of each family member to environmental factors **(**Stevanović and Lakić, 2007).

It is impossible to predict how a parent will react to their child's illness, but there is no parent who will not change by learning about it. This awareness awakens emotions and thoughts ranging from initial shock, anger, sadness, guilt, anxiety, fear, insecurity, uncertainty, and boundless helplessness. There may also be psychosomatic disorders or sleep disorders due to feelings of sadness. Unable to focus on anything unrelated to illness and childcare, they withdraw into themselves and think they will never be happy again. All this consistently leads to stress and trauma for all family members **(**Stevanović and Lakić, 2007; Lindström and Eriksson,1993).

Psychological trauma and physical trauma are the basis of the psychological reaction of the parents there is burnout. The first 6 months or one after the diagnosis of epilepsy. In addition to experiencing the emotional experience of labeling, parents**.** The child experiences the stress of losing his health completely. Uncertain, unexpected seizures and uncontrollable situations reminiscence or association of the event exhausts the family and plunges it into chaos (Mu, 2005). Some types of seizures show frightening features.

Numerous parents regard each tonic or clonic seizure as a life-threatening event. Seizure frequency and duration of seizure, family relations and epileptic**.** It is seen that it affects the adaptation to the conditions negatively (Galletti et.al., 2004). Child and family of epilepsy ıt's effect on daily life depends on some factors. Among these factors severity of epilepsy, complexity of clinical treatment, its meaning on society, restrictions on the activities of the child and family, child and family-specific coping skills, level of social support, epilepy there is a dimension to the available resources about it. Each of these factors is chronic. Contributes to the actual or perceived harmony in the disease **(**Camfield et.al., 2001) Epileptic many of the children's parents have been neglected by many mental health problems are affected by the problem. Regular treatment for such children**.** Applying these methods can affect the mental and physical health of families. Necessary for personal care, leisure activities and other pursuits. İt also takes away time (Thomas and Bindu, 1999). Both protective and rejecting parents attitudes are reported in children with epilepsy. Findings of children with epilepsy know that they show excessive addictions because of their mothers' dominant attitudes (Hodes et.al., 1999).

Mental Symptoms in the Child and Family with Epilepsy

The often ambiguous nature of epilepsy causes patients to experience many psychosocial problems. Psychosocial problems frequently seen in epilepsy patients; stigma, social isolation, problems in interpersonal and family relationships, cognitive dysfunctions, decrease in self-esteem, decrease in school performance. Psychosocial problems can lead to bigger problems than the physical symptoms of the disease. Psychosocial problems associated with epilepsy may depend on the etiology and neuropathology of the disease, age of the patient, frequency, severity and type of seizures, duration of epilepsy, antiepileptic drugs and various psychological factors. Psychosocial problems are especially associated with depression and anxiety in epilepsy patients (Karaca and Durna, 2018).

There is a relationship between uncertainty and sudden loss of control, and depression and anxiety in children with epilepsy and their caregivers (Fritz, 2003). Existing research shows that mothers of children with chronic diseases are more vulnerable to stressors, and that fathers have chronic diseases in their children.

He reports that he is less traumatized when he has an illness. Parents' reactions to childhood illnesses are different. Mothers are personally sacrificing themselves more to their children and may experience a new seizure.

They are more worried than fathers when they start (Shore, 2002). There is a relationship between the severity and frequency of seizures in increasing maternal stress and anxiety levels relationship was found **(**Laybourn and Hill, 2003)**.** A relationship was also found between high levels of anxiety and stress perceived by parents due to addiction to antiepileptic drugs in children with epilepsy (Fritz, 2003).

Coping Attitudes of the Child and Family with Epilepsy

Family coping style is associated with developmental disabilities or adjustments to chronic illness. However, the effectiveness of the methods developed by a family with social labeling in a disease such as epilepsy is especially remarkable.

It is not known how and to what extent what develops proficiency (Mua et.al., 2005). The differences between parents exhibiting good coping and poor coping management have been examined in several studies. better

coping. In the study conducted by Korkmaz et al. (2020), it was reported that the age of the families and the level of health literacy are effective factors on the compliance of children with epileptic drugs (Korkmaz et al., 2020). Lack of adherence to treatment in children with epilepsy increases the frequency of seizures and decreases the quality of life by reducing disease control. Therefore, supporting the family both theoretically and socially is important in increasing treatment compliance and quality of life in children with epilepsy. It is defined as the use of multiple methods to achieve very effective coping. Coping methods used include crying, talking to someone, exercising, asking someone for help, shouting, screaming, slamming the door. Although there are no significant differences between the stressors of mothers and fathers, there are important differences in coping methods. While mothers prefer to occupy themselves with other activities by crying and ignoring the problem, fathers also display the behavior of escaping from the problematic situation (Stephan, 2002).

The most important problem in the treatment of pediatric epilepsy is poor antiepileptic drug compliance. 20-80% of epilepsy patients have poor drug adherence, which leads to poor seizure control, which reduces their quality of life. In order to increase adherence to treatment and disease control in epilepsy, it is necessary to improve the knowledge and awareness of patients and families. In addition, education works well to assist epilepsy patients and their families in managing the many complications they may encounter related to seizures and treatment. In previous studies, behavioral intervention, medical education, drama education and video animation have been used to increase knowledge and awareness. It has been reported that all these educational activities are effective in increasing knowledge and disease control in both patients and families. (Tang et al., 2014; Saengow et al., 2018; Karaca and Durna, 2018).

Epilepsy patients who use coping strategies, have high self-efficacy and have a more positive attitude towards their disease are less likely to encounter psychosocial problems. Therefore, it is very important to provide psychological support as well as medical interventions in the treatment of epilepsy patients (Karaca and Durna, 2018).

Counseling services and cognitive behavioral treatment methods can help epilepsy patients develop more positive attitudes towards epilepsy by increasing their self-efficacy, and also in the management of anxiety and depression (Karaca and Durna, 2018).

CONCLUSION

Childhood epilepsy, like other chronic diseases, affects the whole family because it forces the existing resources of the family. According to the biopsychosocial model, the patterns operating in family relationships affect the mental processes of family members, and the biopsychosocial processes of the sick individual affect the functionality of the family. In other words, epilepsy should not only affect the person with epilepsy.

It also causes the family, which is a unit, to be affected. The family has to face many problems when the child is diagnosed with epilepsy. Although many studies on epilepsy have examined the patient's quality of life and its relationship with his family, few studies have focused on problems with family members resulting from epilepsy.

In conclusion; When epilepsy patients comply with the diagnosis and treatment, they can continue their normal lives and be successful in their daily lives like the people in the general population. For this reason, patients, families, school officials and the society should be constantly informed and negative prejudices should be eliminated. Nurses can play an important role in raising awareness and awareness of individuals, families and society by taking an active role in the organization and implementation of education programs related to epilepsy.

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CHAPTER 8

INTRAUTERINE DEVICES FOR CONTRACEPTION

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INTRODUCTION

Intrauterine device (IUD) is a contraceptive apparatus made of plastic. It is usually T shaped, sometimes wrapped around by copper wire and sometimes embedded by a reservoir releasing progestin. Intrauterine device is the most preferred, long-term, reversible contraceptive method utilized widely all around the world. Intrauterine devices (IUDs) have high contraceptive efficacy while they exert no systemic metabolic effects. Even progestin releasing IUDs have minimal, mostly ignorable systemic effects. Another advantage of IUD is that the contraceptive efficiency is not related to coitus. Taking pills every day or providing condom for every single intercourse is demanding for most of the people which makes IUD an appealing method of long term contraception. Once, the IUD is introduced into the uterus, the contraceptive performance begins and stays intact for the life span of the device. On the other hand, intrauterine device is similar to barrier methods in terms of fertility restoration, once the IUD is removed, the fertility restores immediately.

Although IUD is firstly recognized as a contraceptive device, actually progestin releasing IUD is, also, a treatment method for abnormal uterine bleeding, dysmenorrhea and an adjuvant for estrogen therapy in postmenopausal women.

Contemporarily, all of the modern IUDs need to be removed and replaced within certain intervals. The recommended intervals change according to the amount of copper, progestin or auxiliary material (like Ag for example) they incorporate.

In this chapter we aimed to review, evaluate and compare the efficiency, advantages, disadvantages and side effects of different types of modern IUDs.

1. TYPES OF MODERN IUDS

The T-shaped modern IUD was first designed at 1968 by Hoeward Tatum (Tatum 1983). Tatum designed a device mimicking the shape of the intrauterine cavity in order to prevent cramping and heavy bleeding encountered with earlier IUDs. The polyethylene T shaped plastic frame was embedded to barium sulphate in order to make the device radiopaque. In addition, inspired by Jaime Zipper's idea of boosting IUDs with copper, he added copper wires to the IUD (Zipper, Medel, and Prager 1969). Zipper's

idea was depending on his clinical experiments manifesting the local effects of copper on endometrium. Consequently, the first copper containing T shaped IUD, the CuT-200 was produced (Tatum 1983).

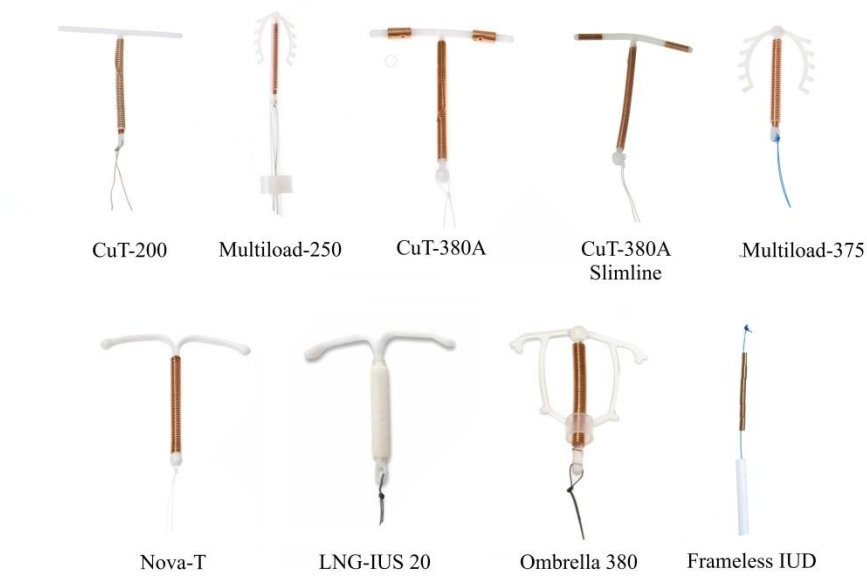

Figure1

First copper IUDs were CuT-200 and Multiload-250, containing 200mm^2 and 250mm^2 copper wire respectively (Figure1). Currently, these IUDs are still manufactured and are accessible in various parts of the world. In modern IUDs, the copper amount was increased and the copper wires were replaced by solid copper tubular sleeves. Likewise, these IUDs have additional augmentation of copper sleeves on the horizontal arms. The effective interval for contraception is longer for these IUDs and replacement intervals are lengthier than IUDs with less copper reserve. Examples for these modern IUDs are CuT-380A, CuT-380slimline, Nova-T and Multiload-375.

CuT-380A is one of the most potent contraceptive IUDs (Figure1). This device has copper sleeves on both horizontal arms in addition to the cooper wire wound around the stem (Sivin and Tatum 1981). The letter "A" in the name of the device is derived from the 'arm' and emphasizes the impact of adding copper on the horizontal arms. It has been marketed in many countries with different trade names all around the world since 1982. CuT-380A's

polyethylene plastic frame has vertical length of 36mm and horizontal width of 32 mm. Copper surface area is 380 mm^2. The electronic copper around the stem weights 176 mg. Copper sleeves on horizontal arms weight 66.5 mg each. A polyethylene monofilament is tied to the 3 mm sized ball at the bottom of the stem. This monofilament comprises two strings facilitating the follow-up and removal of the IUD. The ball shape at the bottom of the stem is designed to decrease the risk of cervical perforation. CuT-380A has clinical approval of 10 years for continuous use by regulatory authorities. It needs to be removed at the end of this period. It is possible to replace it with a new one in the same visit if there is not any contraindication.

CuT-380Ag is a very similar form of CuT-380A. Only the copper wire in the stem contains a silver core in order to prevent fragmentation and extend the life span of the IUD. CuT-380 Slimline has the copper sleeves on the end of horizontal arms (Figure1). This promotes the IUD's loading to the insertion tube and facilitates its placement in the uterine cavity. The contraceptive efficiency of CuT-380Ag and CuT-380 Slimline are similar to CuT-380A (Sivin, Diaz, et al. 1991; Sivin and Stern 1994).

Multiload375 was designed by WAA van Os in 1977 as a combination of positive aspects of Dalkon shield and CuT-380A (Chi 1993) (Figure1). It has 0.4mm copper wire with a surface area of 375mm^2 wrapped around its stem. Its flexible arms with lateral projections are designed to minimize expulsion. It has a monofilament nylon tail for follow-up and removal. It is one of the most popular IUDs all around the world. Multiload 375 is similar to CuT-380A in contraceptive efficiency (Chi 1993).

Nova-T is similar to CuT-200 for dimensions and material of its frame (Figure1). Copper surface area is 200mm^2 as CuT-200. However, Nova-T encapsulate a silver core with a diameter of 0.1mm. Furthermore, it has more flexible arms to prevent IUD from expulsion and a flexible loop at the base of the stem to prevent cervical injury. There are concerns regarding that the contraceptive efficiency of Nova-T declines at the end of 3 years, however Scandinavian cohort studies demonstrated a stable and low rate of pregnancy even at the end of 5 years of continuous use. (Luukkainen et al. 1983).

Addition of a progestin containing reservoir to IUD was targeted to minimize bleeding and cramping associated pain. Initially, a T shaped IUD was developed which was excreting 65mcg progesterone to circulation daily

however since the effective half-life of progesterone was short, it was replaced with levonorgestrel, a more potent synthetic progestin. The contraceptive life span of the IUD depends on the amount of the levonorgestrel encapsulated within the reservoir.

Levonorgestrel containing intrauterine system (LNG-IUS 20), is a T shaped device with a reservoir on the vertical stem (Figure1). The reservoir contains 52mg levonorgestrel embedded in polydimethylsiloxane and releases 20mcg levonorgestrel per day initially. This daily secretion provides 150-200pg/ml of consistent levonorgestrel plasma concentrations (Andersson, Odlind, and Rybo 1994; Luukkainen et al. 1986). The amount of secretion per day decreases gradually and declines to the half of the original value at the end of 5 years. The average plasma concentrations at the end of first year, second and fifth years are 180, 192 and 159 pg/ml respectively (Andersson et al. 1994). It is 32 cm in length, 32 cm in width and the diameter of the insertion tube is 4.4 mm. It is approved for 5 years' continuous use. However, there are reports of safe and efficient performance for 7, even 10 years. (Sivin, Stern, et al. 1991; Toivonen, Luukkainen, and Allonen 1991; Xiao et al. 1990). A large scale study demonstrated similar contraceptive performance and continuity rates for CuT-380A and LNG-IUS 20 (Sivin et al. 1987).

LNG-IUS 20 has been utilized for purposes other than contraception and has some advantages over CuT-380A. First of all, it diminishes blood loss during menstruation (Sivin, Stern, et al. 1991; Toivonen et al. 1991; Xiao et al. 1990). Some studies report that LNG-IUS 20 has similar efficiency as endometrial ablation for treatment of abnormal uterine bleeding (Crosignani et al. 1997; Kaunitz et al. 2009). Furthermore, the local effects of progestin on endometrium is beneficial in tamoxifen using patients (Gardner et al. 2000), in patients with dysmenorrhea (Vercellini et al. 1999) and in postmenopausal individuals receiving estrogen replacement therapy (Hampton et al. 2005). It provides high progestin levels on the endometrial tissue. Subsequently, endometrium cannot proliferate resulting in continuous thin endometrial lining. Consequently, the episodes of bleeding and spotting is reduced and less menstrual blood loss occurs during menstrual period. Amenorrhea and irregular bleeding can be encountered in some individuals in the first 3-6 months of LNG-IUS 20 utilization. At the end of 1 years, 20% of the individuals develop amenorrhea.

There are 19.5mg and 13.5mg levonorgestrel containing forms other than LNG-IUS 20. Levonorgestrel IUD with 19.5mg progestin reservoir secretes 17mcg levonorgestrel per day initially and at the end of 5 years it declines to 7.4mcg/day. It is approved for 5 years of continuous use and only for contraceptive purposes (Creinin et al. 2016). The levonorgestrel IUD with 13.5mg progestin reservoir, releases 14mcg levonorgestrel initially and at the end of 3 years it declines to 5mcg/day. Similarly, it has been approved for 3 years and only for contraceptive purposes (Apter et al. 2014). These less levonorgestrel releasing devices has more gentle insertion tubes with a diameter of 3.8mm. Therefore, they are marketed for and generally preferred by nulliparous individuals.

Additionally, there are devices secreting only 5 or 10 mcg levonorgestrel per day which are manufactured mainly for endometrial protection during postmenopausal estrogen replacement therapy. These devices are approved for 5 years of continuous utilization in postmenopausal individuals (Raudaskoski et al. 2002).

Ombrella 250 and 380 are manufactured as more flexible and more compatible with the shape of the uterus in order to minimize the side effects and reduce the expulsion rate (Figure1). These devices have 250mm2 and 380mm^2 copper wire wound around their stems respectively.

Frameless IUDs are developed beginning from 1980s. The main objective was to minimize the side effects like cramping and excessive bleeding. These are also designed for decreasing the expulsion rates. First of all, Dirk Wildemeersch from Belgium invented the frameless IUD in 1983 (Figure1) (Van Kets et al. 1997; Wildemeersch 2010). It is composed of 6 copper sleeves, containing 330mm2 copper in total, aligned on a surgical nylon string. This string has a hooked pin at one end which gets stuck into the fundal part of the myometrium during insertion and serves as an anchor to prevent expulsion. The frameless design provides extremely low rates of discontinuation due to cramping or bleeding. On the other hand, relatively difficult insertion technique may increase the expulsion at the first place. However, at the hands of experienced clinicians the expulsion rates are very low. These frameless IUDs are suitable for especially nulliparous and nulligravid individuals (Van Kets et al. 1997; Wu and Hu 2000). The popularity of this device is rising constantly.

Recently, a new IUD, releasing 14mcg levonorgestrel daily with a frameless design is being developed for perimenopausal patients (Wildemeersch, Schacht, and Wildemeersch 2003). This device is expected to provide effective treatment for endometrial hyperplasia and excessive uterine bleeding (Wildemeersch et al. 2007; Wildemeersch and Rowe 2004).

2. MECHANISM OF ACTION

The contraceptive effects of all IUDs depend on the foreign body reaction and mainly occur within the uterine cavity. This reaction is believed to be a sterile anti-inflammatory response and causes minor tissue damage which consequently constitutes a spermicidal environment. At the 7 months after IUD insertion, there were a remarkable increase in leucocyte counts of endometrial samples compared to levels before IUD insertion (Cuadros and Hirsch 1972). This extraordinary increase of leucocytes generates the end products of tissue degradation which are toxic against spermatozoa and blastocyst. Subsequently, this inflammatory reaction results in phagocytosis of spermatozoa. The magnitude of the inflammation is positively correlated with the size of the foreign body. It has been demonstrated that very few spermatozoa can reach the fallopian tubes in the presence of an IUD. An innovative study searching for fertilized ovum after sexual intercourse in women with documented ovulation at luteal phase, confirmed that there was no fertilized ovum in tubal irrigation fluids of women with IUD (Alvarez et al. 1988). There are similar reports demonstrating the absence of sperms in fallopian tubes (El-Habashi et al. 1980; Khan et al. 2017). Microscopic studies demonstrate that leucocytes encircle the sperms and phagocyte them. It has been verified that in women with IUD, sperms were phagocyted in endometrial cavity 2-16 hours after intercourse (Sağiroğlu 1971).

Modern IUDs are reinforced with copper since it enhances the inflammatory reaction remarkably (Cuadros and Hirsch 1972). Major mechanism for IUDs comprising copper is the spermicidal capability. However, no measurable increase of copper levels can be detected in serum plasma levels. Studies establish that copper has spermicidal effects on sperms subsiding their motility and impairing the fertilizing capacity. It has been demonstrated in samples collected 24 hours after intercourse, that sperm movements from cervix to fallopian tubes are markedly impaired (El-Habashi et al. 1980). Sperm count in fallopian tubes is significantly less in women with copper IUD (Nelson 2000). In the presence of copper ions, the acrosome

enzymes necessary for penetrating the zona pellucida are not activated (Alvarez et al. 1988). Therefore, even the sperms can meet with the ovum, it is not fertilized most of the time because of these spermicidal effects. (Alvarez et al. 1988). In studies using sensitive hcg assays, the absence of fertilization was documented in women with copper IUD (Segal et al. 1985; Wilcox et al. 1987). These findings are associated with the fact that copper IUDs are protective against both intrauterine and ectopic pregnancies. On the other hand, copper IUD release free copper and copper salts resulting in both biochemical and morphological changes in the endometrium. This increases the production of prostaglandins and cytotoxic peptides in the endometrium, inhibiting the endometrial enzymes (Ammala et al. 1995). By this way, the receptivity of the endometrium is inhibited and consequently, endometrial implantation of fertilized ovum is impaired. Also, copper impairs the vitality of sperms within the cervical mucus (Elstein and Ferrer 1973; Jonsson, Landgren, and Eneroth 1991). In individuals with IUD the cervical mucus sperm count is significantly less than individuals without IUD (Nelson 2000). It is important to note that IUD is not an abortifacient, even when used for emergency contraception and the utilization of both inert and copper IUDs do not impair ovulation. (Ortiz and Croxatto 2007; Sivin 1989)

Progestin releasing IUD exert foreign body reaction with additive local effects of progestin on endometrium. Endometrium is decidualized as a result of atrophy of secretory glands. (Critchley et al. 1998). Progestin IUD possess two possible mechanism of action; the first is inhibition of implantation. The second is inhibition of sperm capacitation, penetration and survival. Progestin IUD users have half of the serum progestin levels of Norplant users and this proves that ovarian follicular development and ovulation are only partially inhibited. At the end of 1 year of continuous usage, in %50-75 of LNG-IUS 20, the cycles are ovulatory independent of the bleeding patterns (Barbosa et al. 1995). Additionally, progestin IUD thickens the cervical mucus and provides a barrier for sperm penetration.

3. EFFICIENCY AND SAFETY

Modern copper IUDs have more than 99% contraceptive efficiency. The 10-year contraceptive efficacy of CuT-380A was found to be as effective as tubal ligation in individuals over 30 years old (Mansour 2007; Peterson et al. 1996; Sivin 2007). Nonetheless, the return of fertility is much easier with removal of the IUD than tubal reversal surgical procedure. At the end of 5

years continuous use, IUD was calculated as the most cost effective contraceptive method (Cromer et al. 2008). In Turkiye IUD users have higher satisfaction and contentment levels than other reversible contraceptive method users (Gavas and İnal 2019). In developing countries, the failure rates in IUD users was detected to be lower than oral contraceptive users (Farr and Amatya 1994).

Tcu380A is approved for 10 years' continuous use. However, it's efficacy at 12 years of continuous use has been established (Rowe et al. 1997). Even, in some observational studies with limited number of unexpectedly long-term users, it is associated with high efficiency with very low failure rates at the end of 20 continuous years of use (Sivin 2007). The proposed and approved time for continuous use is 4 years for CuT-200 and 5 years for Nova-T. LNG-IUS 20 is safe and effective for at least 7 years, and probably for 10 years, although official approval of LNG-IUS 20 is for 5 years (Hidalgo et al. 2009; Sivin and Stern 1994). There are many studies showing that the efficiency of levonorgestrel IUDs releasing 15-20mcg levonorgestrel per day is similar to copper IUD with more than 250mm^2 copper (Sivin, Stern, et al. 1991; Sivin and Stern 1994).

Inert IUDs do not require replacement, however, they cause endometrial irritation as a result of calcium salt deposition at long term use. If abnormal uterine bleeding is present, the inert IUD should be replaced. Today the use of inert IUDS are very limited and most of the clinicians replace them with modern copper or levonorgestrel IUDs.

The overall evaluation of modern IUDs, reveal an average failure rate of 3%, expulsion rate of 10% and discontinuation rate of 15% at the end of 1 year (World Health Organization 1990). The main reason for discontinuation is excessive bleeding and cramping. The rate of failure and discontinuation gradually decrease with increasing age and exposure time. In studies with experienced clinicians and motivated patients, the failure rate for CuT-380A was less than 1% (Chi 1993; Petta, Amatya, and Farr 1994). Discontinuation rates because of adverse effects declined every year for 12 years and the cumulative pregnancy rate was 1.5% for 7 years and only 1.9% for 12 years of continuous use (Rowe et al. 1997; World Health Organization 1990). The cumulative rate for discontinuation at the end of 7 years was 1.6% for failure, 22.7% for bleeding and pain and 8.6% for removal of the IUD. The rate of

discontinuation at the end of 12 years was 1.7% for failure, 35.2% for pain and bleeding and was 12.5% for expulsion of the IUD (Rowe et al. 1997).

LNG-IUS 20 failure rate at the end of 1 year is 0.2%. Five years' cumulative rate for discontinuation of LNG-IUS 20 is 0.5%. The most common reasons for discontinuation were failure with a rate of 5.8% and bleeding and pain with a rate of 13.8% (Andersson et al. 1994).

Naturally in more fertile individuals and in users below 25 years old, the failure rates are higher. The IUD users tend to use IUDs for a longer time than other reversible methods and continuation rates are higher when compared with oral contraceptive pills, condom and diaphragm.

The local endometrial reaction rapidly resolves after the removal of the IUD. The restoration of fertility in both types of, copper and levonorgestrel, IUD users is certain. Timing of desired conception is similar to barrier method users (Vessey et al. 1983). Large studies demonstrate that no delay occurs in achieving pregnancy independent of the exposure time. The incidence of term pregnancy, spontaneous abortion and ectopic pregnancy are similar to non-contraceptive users. This confute the opinions that IUD cause serious infections leading to infertility (Belhadj et al. 1986; Vessey et al. 1983). No significant difference was detected in cumulative pregnancy rates in parous, nulliparous and nulligravid patients (Skjeldestad and Bratt 1988; Wilson 1989).

LNG-IUS 20 can cause a mild increase in the ovarian cyst formation however, these are generally asymptomatic and resolve spontaneously (Inki et al. 2002). No increase in the risk of venous thrombosis was detected in LNG-IUS 20 users (Lidegaard et al. 2009). In some progestin IUD users, an amount of progestin sufficient to cause androgenic side effects like acne and hirsutism, can cross to the circulation. However, in a study serum SHBG levels were not affected and this demonstrates that remarkable clinic effects are highly unlikely (Pakarinen, Lähteenmäki, and Rutanen 1999). In patients with facial androgenic complaint spironolactone is effective and can be prescribed. The dosage can be titrated down to the lowest effective level. There is not any metabolic changes related with glucose metabolism, insulin sensitivity and lipid profile (Morin-Papunen et al. 2008). In a large scale study, breast cancer incidence in LNG-IUD 20 users was found to be similar to the general population (Backman et al. 2005). The combination of low dose progestin-IUD and estrogen therapy was not associated with increased breast

tissue density in postmenopausal individuals (Lundström et al. 2006). The lack of systemic metabolic effects, copper IUD are safer than systemic hormonal contraceptive methods and preferred in individuals with systemic venous diseases (Sivin and Batár 2010).

Some IUD users report increase in the amount of vaginal discharge. These should be examined thoroughly for the presence of vaginal and/or cervical infections. If any infection is detected, treatment can be made while IUD is in place.

Many long term studies demonstrate that IUD use is not associated with an increase in the incidence of endometrial and invasive cervical cancer. Nonetheless, IUD use was associated with a reduction in the risk of these neoplasms after removal (Benshushan et al. 2002; Cramer et al. 1985; Hill et al. 1997; Lara-Torre et al. 2004; Matkovic et al. 1994; Parazzini, Vecchia, and Negri 1992; Pasquale et al. 1997; Sturgeon et al. 1997).

Copper IUDs are not effected by magnetic resonance imaging (MRI), therefore both staff and patients are safe during MRI (Mark and Hricak 1987; Pasquale et al. 1997).

4. ISSUES ABOUT INSERTION

4.1. Time for Insertion

It is widely believed that the optimal time for IUD insertion is at the time of menstrual bleeding. However, there are sufficient data showing that IUDs can be placed at any time of the menstrual cycle. The clinician needs to be sure that the recipient is not pregnant.

4.2. Patient Selection

The most important factor for patient selection is the presence of risk factors for pelvic inflammatory disease (PID). Individuals with multiple sexual partner, alcohol or drug users are generally in high risk group for pelvic infections (Kaufman et al. 1980, 1983). If IUD use is essential, these individuals should use condom regularly for protection against sexually transmitted diseases (STD). The presence of an active PID is an absolute contraindication for IUD insertion.

Additionally, caution must be paid in individuals with excessive menstrual period bleeding because IUDs are expected to increase the amount

of bleeding. Individuals on anticoagulants or ones with coagulation problems are not suitable candidates for copper IUD use. However, these individuals might benefit from progestin IUD. Likewise, patients with uterine anomalies like bicornuate, submucous myoma, cervical stenosis are not suitable for IUD use.

Classically copper IUD are not recommended for individuals with copper allergy or Wilson disease. However, up to date no adverse reaction was reported in these patients associated with IUD use. The daily amount of copper released to circulation is less than the amount consumed by a regular diet (Newton and Tacchi 1990). However, progestin IUD or barrier methods seem to be more suitable in Wilson disease (Haimov-Kochman, Ackerman, and Anteby 1997).

Diabetes mellitus (DM) is mostly a disease of advanced age. Therefore, it is important to note that in both insulin dependent and independent DM, the use of copper IUD has no side effects or adverse effects (Kjos et al. 1994). As a matter of fact, in an individual with DM associated vascular complications, IUD is the ideal method and is preferred against hormonal contraceptives.

Nulliparous and nulligravid individuals can safely use IUDs (Suhonen et al. 2004). The rates of complications like expulsion or perforation are similar with parous users (Suhonen et al. 2004). When nulliparous were compared with parous no significant difference was detected in terms of IUD efficacy and side effects (Duenas, Albert, and Carrasco 1996). The majority of evidence are in favor that IUD use does not have any adverse effects on fertility (Belhadj et al. 1986; Rowe et al. 1997; Skjeldestad and Bratt 1988).

Moreover, IUD should be considered as an alternative method in adolescents. In studies with adolescents the rates of continuation was similar with other women at the end of 1 year (Sanders et al. 2017). IUD can provide long term, safe contraception in these individuals with appropriate screening, counseling and care. In a study held in USA, the continuation rate was 73% at the end of 2 years and was 46% at the end of 5 years in adolescents (Abraham, Zhao, and Peipert 2015; Diedrich et al. 2015).

A detailed bimanual examination and speculum examination is necessary before IUD insertion. The position of the uterus needs to be determined. The most common reason for perforation at the time of insertion

is the presence of undetected extreme posterior flexion of the uterus. However perforation is rare, the incidence is less than 1/3000 (Edelman and van Os 1990).

Uterus larger or smaller than usual can be challenging during IUD insertion. Uterus is better sound between 6-9cm for a problem free IUD use. Ideally, it should be demonstrated that cervix and vaginal infections are not present. IUD insertion needs to be delayed in the presence of mucopurulent cervical discharge or bacterial vaginosis.

4.3. Pain Management During Insertion

One of the major drawbacks for IUD use is pain perception during insertion. Therefore, various methods and medications that might be beneficial to IUD insertion related pain were in the focus of research for decades.

Naproxen in different doses were investigated in different trials. In trials with oral 300 and 375mg naproxen, pain relief was not achieved during insertion. Rather these patients manifested lower pain scores in hours after insertion and required reduced extra analgesic doses (Massey, Varady, and Henzl 1974; Miles, Shvartsman, and Dunlow 2019). However, 550mg oral naproxen was effective for relieving IUD insertion pain compared to placebo (Karabayirli, Ayrm, and Muslu 2012). In a trial investigating oral tramadol 50mg and 550mg naproxen, both were effective for relieving IUD insertion pain when compared to placebo. Tramadol was found to be more effective than naproxen (Karabayirli et al. 2012). Adding 5ml intrauterine %2 lidocaine to oral naproxen did not make any difference in pain scores (Miles et al. 2019).

On the other hand, when oral naproxen 550mg was compared with %2 lidocaine intracervical block, the block was significantly superior to naproxen in pain management (de Oliveira et al. 2021). Non-steroidal anti-inflammatory (NSAID) drugs, other than naproxen, were not proven to be effective for analgesia during IUD insertion. Oral ibuprofen was investigated in doses of 400mg, 600mg and 800mg whereas none of these formulations provided pain relief for IUD insertion related pain (Bednarek et al. 2015; Chor et al. 2012; Hubacher et al. 2006; Jensen, Blaabjerg, and Lyndrup 1998). Similar to lower doses of naproxen intramuscular injection of 30mg ketorolac

provides pain relief at 5 and 15 minutes following IUD insertion but does not reduce pain during insertion (Ngo, Ward, and Mody 2015).

Local gel formulations of %2 lidocaine administered either intracervical or topical does not reduce teneculum related pain and overall pain scores related to IUD insertion (Allen, Raker, and Goyal 2013; Maguire et al. 2012; McNicholas et al. 2012; Nelson and Fong 2013; Rapkin et al. 2016) . Out of the locally administered lidocaine forms, only cream containing 25mg lidocaine combined with 25mg of prilocaine per gram and %10 lidocaine spray locally applied to the cervix provide pain relief during IUD insertion procedure (Aksoy et al. 2016; Tavakolian et al. 2015).

During IUD insertion 10 ml %1 lidocaine paracervical nerve block was found to be an effective method of pain control (Akers et al. 2017). Similarly, in recent studies 1% lidocaine paracervical block was significantly effective in all outcome parameters which were decreased pain with teneculum placement, IUD placement, uterine sounding and pain score at 5th minute after placement (Cirik et al. 2013; Mody et al. 2018). It is important to note that indeed paracervical block itself can be painful, however the reduction in overall pain scores justifies the procedure.

Misoprostol is a prostaglandin analog used to provide cervical dilatation. Thus, researchers wondered intuitively whether misoprostol might provide pain relief by its dilatator effects on cervical canal. Sublingual 400mcg misoprostol eases the IUD insertion scored by the performer, reduces failed attempts and number of difficult insertions although no improvement in pain scores and side effects were demonstrated (Sääv et al. 2007). Sublingual or buccal 400mcg misoprostol did not provide relief (Edelman et al. 2011; Espey et al. 2014; Heikinheimo et al. 2010; Ibrahim and Ahmed 2013). Even in some studies increase in pain scores and side effects were reported (Lathrop et al. 2013). Similarly, vaginal 400mcg misoprostol showed no benefit for pain rather increased side effects and frequency of cramping (Dijkhuizen et al. 2011; Scavuzzi et al. 2013). Vaginal or buccal or sublingual 400mcg misoprostol administration did not provide significant pain relief and was not recommended as a standard procedure in nulliparous woman (Lotke, Tiwari, and Nuño 2013; Swenson et al. 2012).

Dinoprostone have similar effects but fewer side effects than misoprostol. According to a recent meta-analysis of 5 studies, 3mg vaginal dinoprostone was effective in providing pain control during teneculum

placement, uterine sounding, IUD insertion, reduced need for additional analgesia, increased both patient and provider satisfaction and the side effects were not increased as in misoprostol studies (Abu-Zaid et al. 2021).

Consequently, only a limited number of pharmacologic agents yield favorable pain control. These are 550mg oral naproxen, 50mg oral tramadol, some lidocaine formulations including 10% spray, 1% paracervical block and prilocaine added cream form and 3 mg vaginal dinoprostone.

Alternative interventions other than pharmacologic agents were also investigated. Aromatherapy with lavender inhalation decreased the anxiety levels during the procedure (Shahnazi et al. 2012). Verbal analgesia was found to be effective as oral tramadol in nulliparous women (Daykan et al. 2021). Recently, LI4 acupuncture was also found to be effective in lowering IUD insertion related pain scores (Erdoğan and Yardımcı 2023).

It is important to provide efficient pain control to receivers during IUD insertion. Alternative interventions along with pharmacologic agents better be offered during the procedure.

4.4. Prophylactic Antibiotic Use

Primitive IUDs, especially Dalkon shield was documented to be associated with upper genital tract infection, septic abortions and systemic sepsis related deaths. Therefore, this unpleasant experience lead to a serious prejudice against IUD use, raising serious concerns about PID. Researchers were focused on prophylactic antibiotic use prior to IUD insertion in order to prevent subsequent mortal infections.

Doxycycline 200mg oral administered during IUD insertion provided 31% reduction in the rate of unplanned IUD related visits, however no significant difference was detected in PID rates between groups (Ladipo et al. 1991; Sinei et al. 1990; Walsh et al. 1994). Similarly, in a case controlled study with oral doxycycline the incidence of PID and other febrile complications were similar between groups (Zorlu et al. 1993). Azithromycin, 500mg oral, given 1 hour before IUD insertion did not significantly reduce the rate of PID and overall removal rate within 3 months (Walsh et al. 1998).

Consequently, a meta-analysis including 6 clinical trials resulted in the conclusion that prophylactic antibiotics during IUD insertion on low risk populations is unnecessary (Grimes, Lopez, and Schulz 2012). Paying

attention for aseptic conditions during IUD insertion, adequate follow-up with appropriate intervals and convenient manipulations when necessary is superior to prophylactic antibiotic use and seems to be the best intervention to prevent IUD related PID, especially in low risk settings.

4.5. Perforation

The most serious complication about IUD use is the perforation of uterine fundus. Perforation always occurs during insertion (Bromham 1993).

In a large multicenter study the rate of perforation during the insertion of CuT-380A is 1 in 3000 insertions (Heartwell and Schlesselman 1983). Serious complications like intraperitoneal adhesion and intestinal obstruction were reported. All IUD replaced out of the uterus should be removed even they are asymptomatic. Laparoscopic removal can be preferred unless serious intraperitoneal adhesions developed.

5. DISADVANTAGES AND SIDE EFFECTS OF IUD USE

There are some disadvantages and side effects although IUD use is easy, safe and effective method of contraception. The most important factor that diminishes the effectivity is expulsion. Besides pregnancies can occur while IUD is in appropriate place. The management of intrauterine or ectopic pregnancies with appropriately located or dislocated IUD is an important issue. Most frequent side effects are bleeding, pain and infections.

CuT-380A and progestin-IUD do not pose an increased infertility risk following the removal after a good insertion technique and effective counseling and follow-up (Hov, Skjeldestad, and Hilstad 2007). Fertility rates are normal even IUD was removed for reasons like abnormal bleeding or cramping (Belhadj et al. 1986; Vessey et al. 1983).

5.1. Expulsion

Approximately 5% of the patients expulse the CuT-380A spontaneously during the first year of use. This rate is higher in individuals younger than 20 years old (Rivera, Chen-Mok, and McMullen 1999; World Health Organization 1990). The cumulative expulsion rate for LNG-IUS 20 was 8% in an adolescent group (Gemzell-Danielsson et al. 2017).

Expulsion is generally associated with vaginal discharge, cramping pain and/or uterine bleeding. In some instances, there is no symptoms and

expulsion is suspected via the observation of longer than usual or absent threads. If expulsion is suspected, the patients should refer to medical counseling as soon as possible. Dislocated IUDs should be removed. Unless there is pregnancy or infection, a new IUD can be inserted.

5.2. Pregnancies with IUD

5.2.1 Ectopic Pregnancy

Being a previous IUD user does not increase the risk of subsequent ectopic pregnancy and being a present IUD user is protective against ectopic pregnancy (Edelman and van Os 1990; Gemzell-Danielsson et al. 2017; Skjeldestad 1997; Wilson 1989; World Health Organization 1990).

In a large multicenter study, the authors concluded that IUD users are likely to have ectopic pregnancy with 50% less probability than non-contraceptive users (Sivin 1991) . This protection was not as high as suppression of ovulation by oral contraceptive use. For that reason, although the efficiency of CuT-380A and progestin-IUD in preventing pregnancy is very high, if an individual is detected to be pregnant while IUD in situ, the probability of that pregnancy being ectopic is more likely. However, ectopic pregnancy in an IUD user is a very rare incident.

In USA the rate of ectopic pregnancy in non-contraceptive users is 3.25-4.5/1000 women years. In CuT-380A users, total pregnancy rate is 3.4/1000 women years and ectopic rate is 0.2-0.4/1000 women years (Sivin 1991). Ectopic rate with LNG-IUS 20 is 0.2/1000 women years (Andersson et al. 1994). Therefore the relative risk for ectopic in IUD users is 0.1 less than non-contraceptive users (Sivin 1991).

The lowest ectopic pregnancy rates are associated with most effective IUDs, for example CuT-380A has 90% less probability for ectopic pregnancy than non-contraceptive users (Sivin 1991). This is 10 times less than the probability with less copper containing IUDs like Tcu200 (Sivin 1991). In a large study with CuT-380A only one ectopic for 8000 women years was reported. Also ectopic pregnancy associated with LNG-IUD 20 is a very rare incident. Only 4 ectopic pregnancies out of 6 total pregnancies were reported in 3 years in a study with 1714 patients (Eisenberg et al. 2015). Five year cumulative pregnancy rate was 0.5% and the 53% of these were ectopic pregnancy (Sivin 2007; World Health Organization 1990).

In conclusion the rate of ectopic in individuals using CuT-380A or LNG-IUS 20 is extremely low compared to non-contraceptive users. However, if a pregnancy occurs while using these devices it is likely to be an ectopic (Backman et al. 2004). The risk of ectopic pregnancy is 3 fold increased in individuals conceived while IUD is in utero when compared to non-contraceptive users After the removal of the IUD the rates are similar to non-contraceptive users (Chow et al. 1986).

Since the high protection rate against ectopic provided by these IUDs, these are preferred contraceptive methods for individuals with previous history of ectopic pregnancy as well.

5.2.2. Spontaneous abortion

Spontaneous abortus is more frequent in individuals conceived while IUD is in utero. Approximately 50% of these pregnancies result with spontaneous abortion. This is 3 times higher than the pregnancies without IUD (Tatum, Schmidt, and Jain 1976; Vessey et al. 1974). For this reason, when pregnancy is diagnosed, the IUD should be removed if the threads are visible. If the continuation of the pregnancy is desired intrauterine instrumentation should be avoided. However, under ultrasonic guidance the rupture of membranes can be prevented (Stubblefield, Fuller, and Foster 1988). The rate of spontaneous abortion after the removal of IUD with visible threads is 20-30% (Alvoir 1973; Lewit 1970; Tatum et al. 1976). This is very close to the spontaneous abortus incidence in the general population.

In early stages of gestation, IUDs without visible threads can be removed using CO_2 or saline hysteroscopy with USG guidance (Assaf et al. 1992; Cohen et al. 2017). If IUD is removed without trauma in the first trimester, the risk of spontaneous abortus does not increase (Foreman, Stadel, and Schlesselman 1981).

The incidence of fetal death is not increased in gestations while IUD is in utero.

5.2.3. Septic abortion

There is no evidence with IUDs other than Dalkon shield that the septic abortus risk is increased (Williams, Johnson, and Vessey 1975). In USA no fatality was reported in pregnancies with IUD left in utero (Fulkerson Schaeffer et al. 2019).

There is no evidence that modern IUDs with monofilament threads cause sepsis during gestation.

5.2.4. Congenital anomalies

No evidence is present demonstrating any congenital anomaly in fetuses exposed to plastic, copper containing or progestin releasing IUDs. Congenital malformation rate is not increased in infants born from individuals conceived while using IUD (Fulkerson Schaeffer et al. 2019; Williams et al. 1975). There is a case control study demonstrating no extremity deformity with IUD use (Layde et al. 1979).

5.2.5. Preterm labor

Preterm labor is 2 fold increased in pregnancies with IUD left in utero (Fulkerson Schaeffer et al. 2019). Another study demonstrated a 4 fold increased rate of prematurity in pregnancies with IUD left in utero compared to pregnancies IUD removed (Tatum et al. 1976).

5.3. Uterine bleeding and Cramping

In the first year following insertion 5-15% of the individuals discontinue for various reasons. The most common reason for discontinuation of copper containing IUD is heavy or prolonged bleeding and intermenstrual bleeding.

Smaller copper IUD and progestin releasing IUDs have significantly lower rates of bleeding and pain. However, in individuals consulted for IUD use, menstrual pattern should be evaluated carefully. Individuals with heavy and prolonged bleeding and/or ones with pronounced dysmenorrhea might not tolerate copper IUDs. Nonetheless, they might benefit from progestin IUD (Istre and Trolle 2001; Tang and Lo 1995).

CuT-380A causes a 50% increase in amount of menstrual blood loos and the menstrual duration prolongs 1-2 days (Milsom et al. 1995). This lasts as long as the IUD is left in place (Milsom et al. 1995). The increased amount of blood loss during the menstrual period following the insertion of the IUD should be treated with reassurance, systemic prostaglandin synthase inhibitors and oral iron supplementation. Generally, bleeding subsides as the uterine cavity gets used to the IUD. For one year period this amount of blood loss usually does not cause iron deficiency however a decrease in serum ferritin

levels is observed for long term use (World Health Organization 1994). Especially in individuals with a desire of long term IUD use and risk factors for iron deficiency and anemia, necessary evaluations should be undertaken. In populations with high prevalence of iron deficiency iron depletion takes place more quickly and iron replacement should be prescribed (Hassan, El-Husseini, and El-Nahal 1999).

NSAIDs can be prescribed to reduce the amplitude of pain and amount of bleeding because the cramping and bleeding is most severe especially in the first few months following insertion. NSAIDs provide benefit even in following cycles with heavy bleeding and severe cramping (Cameron et al. 1990). NSAID medication should be started with the onset of menstruation and last for at least 3 days. Menstrual blood loss can be reduced by using 500 mg mefenamic acid 3 times daily during menstrual period (Anderson et al. 1976). In spite of this therapy if heavy bleeding continues, IUD should be removed. If individual still desires IUD for contraception progestin-IUD should be considered.

LNG-IUD 20 cause an approximately 86% decrease in the amount of blood loss (Andersson and Rybo 1990). Amenorrhea can develop in time while using LNG-IUD 20 because of the decidualization and atrophic effects on endometrium. At the end of 2 years 70% of LNG-IUD 20 users are oligomenorrheic, 30-40% are amenorrheic (Andersson and Rybo 1990; Backman et al. 2000).

In individuals using LNG-IUS 20 for more than 12 years, the rate of amenorrhea is 60%, infrequent and scant bleeding is 12% and regular light bleeding is 28% (Baldaszti, Wimmer-Puchinger, and Loöschke 2003). For some individuals, amenorrhea is not acceptable and this serves as a reason for discontinuation. However, this situation provides a significant increase in serum hemoglobin and ferritin levels eventually (Luukkainen et al. 1986; Sivin et al. 1987).

Intermenstrual bleeding and spotting during IUD use is not infrequent. However, although disturbing, this condition does not cause a significant amount of blood loss. In the presence of an intermenstrual bleeding routine gynecologic examination should be performed to rule out cervical and endometrial pathologies.

5.4. Infections

It is not expected that low risk individuals for STD develop PID during IUD use (Lee, Rubin, and Borucki 1988). Individuals who pose high risk for STD however should be encouraged to use condoms regularly if IUD use is obligatory.

IUD related bacterial infections are associated with the contamination of endometrial cavity during insertion. The classic study of Mishell demonstrated that uterine cavity is contaminated with bacteria routinely during insertion (Mishell et al. 1966). Mishell performed a study analyzing the aerobic and anaerobic cultures of endometrial samples obtained from individuals undergoing vaginal hysterectomy 4 hours to 7 months after IUD insertion (Mishell et al. 1966). In first 24 hours following IUD insertion, endometrial cavity, normally sterile, was found to be colonized by bacteria. In 80% of the individuals undergoing hysterectomy at least 24 hours after IUD insertion, the uterine cavities were found to be sterile suggesting that natural defense of these individuals wipe off the bacteria. All of the endometrial cultures and the string of the IUD obtained after 1 months of IUD insertion were totally sterile (Mishell et al. 1966). The infections occurring after 3-4 months after the insertion are thought to be the result of acquired STD rather than the direct result of IUD. Therefore, early infections that are associated with insertion are polymicrobial with predominance of anaerobes and endogenous cervicovaginal flora. In a meta-analysis of all studies listed in WHO database it was concluded that PID risk was 6 fold higher in the first 20 days than all times and more importantly PID was very rare after the first 20 days of insertion (Rowe et al. 1997). Only 81 PID was diagnosed out of 23000 insertions corresponding to a rate of 0.5 per 1000 women years (Rowe et al. 1997).

The incidence of infection was not different among users of classic inert IUD, copper IUD and progestin IUD. However, there are finding that progestin IUD decrease PID incidence (Andersson et al. 1994; Toivonen et al. 1991). These findings confirm the findings of earlier studies reporting that long term IUD use does not increase the infection risk (Cramer et al. 1985; Kaufman et al. 1983). Infection can be eliminated and minimized with careful follow up and aseptic insertion technique. Even individuals with insulin dependent diabetes does not pose increased risk regarding infection (Skouby, Molsted-Pedersen, and Kosonen 1984).

It is not recommended to place IUD in individuals with a history of recent gonorrhea or chlamydia infection. Because IUD insertion in these individuals might cause transport of pathogens from lower genital tract towards the upper genital tract resulting in salpengitis and PID. Cultures should be taken and IUD insertion should be delayed until the treatment is complete if active endocervical infection is present or suspected. Copper IUDs are associated with lower antichlamydial antibody levels (Lukes, Reardon, and Arepally 2008; Mehanna et al. 1994; Xiao et al. 1990). In vitro copper inhibits endometrial chlamydia growth. Asymptomatic patients with positive cervical cultures for gonorrhea or chlamydia, treatment can be undertaken without removing IUD. However, if findings reveal that infection has reached fallopian tubes or endometrium, treatment should be initiated immediately and IUD should be removed.

Diagnosed bacterial vaginosis should be treated with metronidazole 500mg for 7 days and unless PID is present, IUD can be left in place. No evidence shows that bacterial vaginosis incidence is effected from the presence of IUD (Shoubnikova et al. 1997). In simple endometritis with only symptom of uterine tenderness on physical examination doxycycline 100mg for 14 days is enough. If tubal infection findings like cervical motion tenderness, abdominal rebound tenderness, adnexial tenderness or palpation of mass or elevated WBC and sedimentation rate are present, then parenteral treatment should be initiated and IUD should be removed once the serum antibiotic levels reach therapeutic levels. Previous IUD use does not change or effect PID treatment.

Recommended regimen for outpatient treatment of mild infections is single dose of cefoxitin (2g, IM) plus probenecid (1g, oral) combined with doxycycline (100mg oral) for 14 days. Alternative regimen is single dose ceftriaxone 250mg IM combined with doxycycline (100mg oral) for 14 days.

Severe infections require hospitalization. Recommended regimen is cefoxitin (2g IV) or cefotetan (2g IV) combined with doxycycline (100mg, oral) for at least 14 days. Alternative regimen is clindamycin (900mg IV, 3x1) combined with gentamycin (2mg/kg IV or IM followed by 1.5mg/kg maintenance dose daily).

Levofloxacin regimens are not recommended any more except in individuals with serious penicillin allergy. If it is to be utilized the

recommended regimen is single dose azithromycin (2g) combined with levofloxacin (500mg oral) for 14 days.

Previously, it was thought that IUD was not suitable for individuals with high risk for bacterial endocarditis (presence of previous endocarditis, ones with rheumatoid valve disease or prostatic valve). However, the bacterial contamination of the endometrial cavity during insertion is very short lived (Mishell et al. 1966). Only in one study findings in favor of bacteremia was demonstrated in the blood culture and this was very short lived and was present only in a few patients (Murray, Hickey, and Houang 1987). In a review with individuals with cardiovascular disease IUD insertion was not found to be associated with endocarditis (Suri et al. 2008; Vu et al. 2016). IUD is a safe and effective way of contraception in patients carrying risk of endocarditis.

The relation between actinomyces infection and IUD use is obscure. There are several case reports addressing unilateral pelvic abscess formation incorporating gram positive actinomyces bacteria (Sawtelle, Chappell, and Miller 2017). Actinomyces is normally a part of gastrointestinal flora and if special caution is spent by pathologists, it is encountered in Pap Smears of 30% individuals with inert IUDs (Fiorino 1996). This rate is much lower (1-7%) in copper or progestin IUD users yet it increases as the exposure time to IUD increase (Merki-Feld et al. 2000). Moreover, actinomyces can be detected in 3% of individuals without IUD (Persson et al. 1984). When actinomyces was detected on Pap Smear, only close follow up with IUD in place is recommended in asymptomatic individuals. The IUD can be removed safely and replaced with a new one without any side effects. In case of uterine tenderness or pelvic mass, IUD better be removed following the initiation of oral penicillin 500mg 4x1 for at least 1 month. Alternative regimen is doxycycline 100mg 2x1 and amoxicillin/clavulonate 500mg 2x1.

Another anaerobe gram positive rod, Eubacterium nodatum, is identical to actinomyces and have been associated with IUD colonization (Hill 1992). In Pap Smear, Eubacterium nodatum can be confused with actinomyces. Treatment and follow up recommendations are similar.

Some cross sectional data indicate that HIV transmission from man to woman is higher in IUD users, especially if IUD is removed or inserted during active exposure to infected individual (Lowry et al. 1989). However, this was not confirmed with following studies (Kapiga et al. 1998). Individuals

infected with HIV are not at higher risk for PID or disease progression than controls (Sinei et al. 1998; Stringer et al. 2007).

Hepatitis C is a sexually transmitted virus. In a study held in Turkiye, it was demonstrated that IUD use does not increase HCV seropositivity (Ozgun et al. 2009).

CONCLUSION

IUDs are proven to be safe and effective for long term, reversible contraception. IUD is a beneficial method for individuals who completed their family. It has many advantages and is the most preferred type of contraceptive in many countries. It is the method of choice in individuals who do not want permanent sterilization, who do not want or who possess contraindication for the use of other reversible contraceptive methods.

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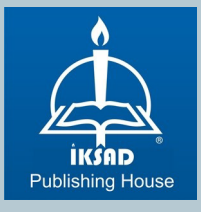

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