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Turkish Medical Student Journal (TMSJ) is the first scientific journal in Türkiye to be run by medical students and to publish works of medical students only. In that respect, TMSJ encourages and enables all students of medicine to conduct research and to publish their valuable research in all branches of medicine.

Turkish Medical Student Journal publishes researches, interesting case reports and reviews regarding all fields of medicine. The primary aim of the journal is to publish original articles with high scientific and ethical quality and serve as a good example of medical publications for those who plan to build a career in medicine. TMSJ believes that quality of publication will contribute to the progress of medical sciences as well as encourage medical students to think critically and share their hypotheses and research results internationally.

The journal is published every four months. The language of the publication is English.

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Editorial

Empowering Medical Students: Celebrating the Diverse Contributions of the June 2023 Issue

Dear Readers,

It is with great pleasure that we present to you the June 2023 issue of the Turkish Medical Student Journal-a vibrant collection of scientific exploration, critical analysis, and clinical insights.

This edition is comprised of three original research articles, four review articles, and two case reports. The diversity of content within this issue exemplifies the multidimensional nature of medical education, where knowledge intertwines with curiosity, and experience intertwines with innovation.

The three original research articles featured in this issue serve as a testament to the tenacity and intellectual acumen of medical students. By engaging in original research, these students have embarked upon a journey that not only broadens the boundaries of medical knowledge but also fosters a spirit of inquiry and analytical thinking. Their dedication to advancing medical science is inspiring and reaffirms our belief in the boundless potential of young minds.

The four review articles delve into diverse medical topics, providing comprehensive synopses of current research and evidence-based practices. By distilling complex concepts into accessible narratives, these articles empower readers with a broader understanding of key subjects, allowing them to bridge the gap between theory and clinical application. We applaud the authors for their meticulous efforts in synthesizing existing knowledge, enabling medical students to navigate the vast sea of information.

The two case reports add a valuable clinical perspective to this issue. By sharing their clinical experiences, the authors not only enrich the collective learning of medical students but also contribute to the vast repository of medical knowledge, fostering a culture of shared learning and continuous improvement within the medical community.

We extend our sincere gratitude to the authors for their commitment to scholarly excellence and the rigorous peer-review process that ensures the quality and validity of the published articles. The diligent efforts of the editorial board and reviewers play a pivotal role in maintaining the journal's academic integrity and upholding the high standards of the Turkish Medical Student Journal.

To the medical students who have contributed to this issue, we salute your dedication and commend your intellectual curiosity. Your passion for knowledge and commitment to the advancement of medical science are the driving forces that propel our profession forward. Through your research, critical analyses, and clinical observations, you embody the future of medicine-an era shaped by innovation, empathy, and evidence-based practice.

Sincerely,

Beliz Koçyiğit
Editor-in-Chief, Turkish Medical Student Journal
Trakya University School of Medicine, Edirne, TÜRKİYE

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REVIEW

RELATIONSHIP BETWEEN OBESITY, BODY IMAGE, SELF-ESTEEM AND CYBER VICTIMIZATION

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ABSTRACT

Bullying is described as a pattern of repeated acts of violence committed against victims due to an imbalance of power. With the development of digital communication technologies like the internet and mobile phones, a new form of bullying known as "cyberbullying" has emerged. Cyberbullying is the intentional, recurrent, and harmful behavior of people or groups using communications technologies. Social media users are vulnerable to cyberbullying due to the independence of its users in terms of choosing when and what to post. Self-esteem is a concept related to how a person perceives themselves in terms of appearance, relationships, success in school and business life, and complete competence and worthiness. Low quality of life, being overweight, athletic inadequacy, and social relationship disorders may cause a decrease in self-esteem in children and adolescents. Lack of confidence and various psychological issues are caused by low self-esteem. Obesity is a chronic illness, and the negative perceptions of obese people held by the public harm such individuals' relationships with others and lower their self-esteem. On social media, people who are obese often get mocking comments about their looks. Children who are overweight or obese are more likely to experience verbal, relational, and physical bullying than their normal-weight peers. Due to the stigma and discrimination associated with obesity, as well as the increased visibility of offensive comments or images through social media, weight-based victimization in online environments can have a negative impact on adolescents' psychological and physical health. Teenagers who have experienced cyberbullying are more likely to believe their bodies are "too fat" than those who have not. Cyberbullying is linked to a wide range of physiological and psychological issues. The prevalence of depression, stress, and suicidal thoughts has increased among obese people as a result of cyberbullying. Obese girls are victims of bullying at a significantly higher rate than obese boys. Various options, such as social and professional help and support groups can prevent the damage to self-esteem in the overweight and obese groups. Internet addiction and cyberbullying can be prevented by conscious internet use, informing children and adults, and parents restricting the internet use of their children. This review examines the relationship between cyberbullying and obesity while emphasizing its causes and results.

Keywords: Body image, cyberbullying, obesity, self-esteem

INTRODUCTION

With the development of new communication technologies, electronic devices, and the internet are now found in all areas of our lives. Young individuals particularly see electronic communication tools as an important part of their social life. Despite technology being a tool that facilitates the fulfillment of daily tasks, a new form of peer bullying encountered in the virtual environment called cyberbullying has been introduced. Being independent in choosing which content to interact with, the amount of time spent on platforms, and having two-way communication make social media users vulnerable to cyberbullying. Cyberbullying is a deliberate, repetitive, and damaging behavior for individuals or groups using communication technologies. It includes threats, harassment, humiliation, sharing inappropriate content, and insulting behavior. Cyberbullying causes the number of victims to be higher than traditional bullying since concepts such as time, space, and physical strength are nonexistent. Additionally, easy access to the target individual and the concealment of the identity of the cyberbully make the act of cyberbullying more prevalent (1). Previous research examining

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the relationship between body mass index (BMI) and peer victimization discovered that children who are overweight or obese are more vulnerable to verbal, relational, and physical bullying than children who have a healthy weight (2, 3). In cyberspace, there is an obvious risk of stigma and victimization for those who are obese or overweight. In a study on school-aged adolescents seeking treatment for weight loss, more than half of the participants stated that they have encountered weight-based cyberbullying on computers or mobile devices. Sixty-one percent of these young people were exposed to embarrassing comments, while 59% were sent upsetting messages or emails (3). According to a study on residential patients with severe obesity, obese adolescents are more likely to be bullied online than their peers who have normal weight (4). Teenagers who have experienced cyberbullying are twice as likely to believe their bodies are "too fat" than those who have not (5). Additionally, body dissatisfaction is related to cyberbullying victimization (5). Adolescents' psychological and physical health can be affected negatively by weight-based victimization in online environments due to the stigma and prejudice associated with obesity, as well as the increased visibility of offensive comments or images through social media (6-8).

We aimed to compile the literature that explores the relationship between cyberbullying, obesity, self-esteem, and body image to deliver the results identified.

DEFINITION OF SELF-ESTEEM

Self-esteem, a multidimensional concept of competence and worthiness, is strongly influenced by how individuals perceive themselves in various aspects such as physical appearance, social relations, success in school and business life (9). Self-esteem progresses from infancy to death and is affected by positive or negative events in the person's experience. Especially in infancy and childhood, the relationship with the mother enables the individual to gain self-esteem as well as a sense of trust. Mother's love in infancy grants the individual feelings of being liked and loved. These feelings are developed in childhood with friends and teachers. If the individual can communicate adequately and positively with friends and teachers during childhood, self-esteem increases. While supporting and admiring children in social relations increase self-esteem, being compared to others and not being supported reduce self-esteem. In the transition to adolescence, individuals begin to know themselves and become aware of their values. With adolescence, self-esteem develops as the personality is established (10, 11).

THE RELATIONSHIP BETWEEN OBESITY AND SELF-ESTEEM

Obesity is a chronic disease and how the society perceives obese individuals damage both their social relations and self-esteem. Persons who are overweight or obese are stigmatized as "slobs", "fatties", and "people who lack self-control and willpower". This dominant and negative automatic response establishes a basis for discrimination (12). Since being thin is appreciated in societies that have adopted a Western way of thinking, overweight individuals are often excluded from society (12). In narrative studies, some people expressed discomfort and disgust when they were seated next to overweight or obese people on buses, trains, or at events (12, 13). This causes obese individuals to feel negative about their bodies and have negative self-concepts (13).

Cameron (14) and Hesketh et al. (15) listed social and environmental communication disorders, being overweight, exclusion, and stigmatization among the causes of low self-esteem, stating that obese adolescents and children have lower self-esteem compared to other individuals (16). Low quality of life, being overweight, athletic inadequacy, and social relationship disorders cause a decrease in self-esteem in children and adolescents (17). A parallel increase in self-esteem was not observed in obese children and adolescents who lost weight and achieved their healthy weight, indicating that obesity is not the sole factor affecting self-esteem (17, 18). Allen et al. (19), who interviewed both overweight and normal-weight children between the ages of 7-13, determined that low self-esteem is not only a result of weight but also a result of body discontent and low self-confidence. Strauss (20) observed obese and normal-weight children for 4 years. Before starting the study, the self-esteem of obese and normal-weight individuals was high and similar. After 4 years, body esteem of obese girls and boys was found to be lower than that of normal-weight boys and girls. Some studies demonstrate that the increase or decrease in body esteem is not only related to BMI, but to several different factors (16, 21-23). The age group in which the relationship between body esteem and body weight is the most significant is adolescents (16). It has not yet been clarified whether low self-esteem is the cause or the result of obesity. Low self-esteem also has many psychological consequences (21). Relationship status and employment are among the determining factors of self-esteem in obese individuals (10). Increased body dissatisfaction is associated with lower self-esteem and increased levels of depressive symptoms (24). Being female, unemployed, obese, and single has been found to be associated with increased body dissatisfaction (25-27). Body dissatisfaction in obese individuals is related to how they perceive their bodies rather than their actual body weight (27). Therefore, focusing on improving the patient's body image may be an integral part of obesity treatment (27). Given the number of factors affecting lower self-perception, a multidisciplinary treatment approach may be necessary when treating patients with obesity. Another reason for low self-perception is the concerns that obese individuals have about their weight (28). Emotions such as sadness, joy, and anger may alter eating habits, digestion, and feeling of hunger in obese and healthy-weight individuals. However, an association between stressed-related eating and increased body weight has been reported (29). Additionally, uncontrolled eating is strongly associated with obese status (30).

Individuals with a positive self-perception can communicate well with other people in their social lives and be more successful in their school or business lives, while those with a negative self-perception are often anxious, restless, and have lower self-confidence (27). Self-esteem is reflected in the behavior of individuals regarding how they perceive their abilities and self-worth at every stage of their life (31). Individuals with a strong sense of self can more easily transfer their talents to their social lives and be successful (31). Self-perception is a concept with many aspects, not only dependent on body weight but also determined emotionally, cognitively, and physically (32).

THE CONCEPT OF CYBERBULLYING AND CYBERVICTIMIZATION

Bullying committed online is referred to as "cyberbullying". Bullying of this nature is common on social media, messaging services, gaming platforms, and mobile devices. It is a pattern of behavior meant to frighten, enrage, or humiliate the targets. Examples include spreading false information about someone, publishing embarrassing pictures on social media, sending offensive or threatening messages on messaging apps, and sending hurtful messages to others while using another person's identity. It is to disturb, humiliate and gossip about other users through internet services, which began with the spread of social media platforms such as Facebook, Twitter, and Skype. Cyberbullying is frequently seen in schools and has become an alarming behavioral disorder and problem in recent years (33). Threats to youth and adolescent health such as eating disorders, anxiety, depression, suicidal tendencies, anger, aggression, and addiction to alcohol, cigarettes, and other substances are shown to be directly or indirectly related to cyberbullying and victimization (9, 10, 34).

THE RELATIONSHIP BETWEEN TRADITIONAL BULLYING, CYBERBULLYING, CYBERVICTIMIZATION AND OBESITY

Cybercrime has two components: The bully and the victim. Victims may be passive or provocative. Provocative victims are those who are more likely to become bullies later in life. Some of the biggest consequences of internet addiction and cybercrime are physical diseases, especially obesity. Improper use of the internet may reduce the time devoted to sports, reading books, or engaging in different activities. Additionally, young individuals' health may be endangered by the occurrence of physical ailments. Using the computer obliquely for a long time may cause postural disorders. Looking at a screen for a prolonged time may cause eye problems, and being sedentary may lead to obesity, insomnia, circulatory problems, and financial problems. Such occurrences may disrupt one's business, academic and social life. Accordingly, it can be concluded that the use of the internet at the level of addiction may cause obesity (35). Overweight students being made fun of by their peers is a common occurrence in schools. In addition to peers, mocking coming from family members may cause emotional problems to increase. Being overweight can decrease self-esteem, increase depression and even cause suicidal thoughts in adolescents (9). As cyberbullying is potentially more dangerous than traditional bullying in this era, problems faced by obese individuals may continue to increase in the near future (35). The severity of depressive symptoms observed in obese girls who had friends who consoled them, showed close attention, and emphasized their competence after being mistreated by their peers was lower than the severity of the depressive symptoms of obese girls who did not have friends to support them (28). Although the mitigating effect of social support was not observed in obese boys with depressive symptoms in the study, social support for individuals who were exposed to cyberbullying may reduce the psychological impact on individuals (9). In a study on the relationship between bullying and body weight, Griffiths et al. (36) reported that obese boys tend to engage in bullying more than normal-weight boys. Obese girls, on the other hand, are victims of bullying at a significantly higher rate than their normal-weighted peers (37). It was reported that boys who did not have normal weight (overweight, obese, and underweight) are victimized more often (37). Thirty percent of boys who are overweight and 31% of boys who are obese are victims of bullying (37). Twenty-three percent of school-age adolescents who had normal body weight were reported to be teased about their weight, while 17% of underweight students experienced weight teasing (38). Teenagers who are underweight, overweight, and obese are more likely to experience persistent bullying than their normal-weight peers (37, 38). For girls, looks and lack of close friends are the most common reasons for being bullied (36). It was stated that 25% of girls who were overweight and 34% of those who were obese were victims of bullying (36). Guo et al. (39) reported that overweight and obese children are particularly vulnerable to verbal bullying. In a study by Janssen et al. (40) examining the relationship between obesity and exposure to bullying with 5749 obese and overweight girls and boys in the 11-16 age group, it was seen that obese and overweight youth between the ages of 11-14 were victims of bullying more than those of normal weight. It has also been observed that people aged 15-16 are more often the bully than the victim. While girls used relational bullying such as exclusion and spreading untrue rumors, boys used both relational and overt bullying, including acts such as verbal-physical assault, name-calling, and teasing. In a study by Lee et al. (41), the effects of traditional bullying and cyberbullying on obese individuals were compared. The study indicated that while both cyberbullying and traditional bullying affected the relationship between BMI and psychological distress, only the effects of traditional bullying were significant. This may indicate that obese or overweight children who have been victims of traditional bullying are more likely to suffer from increased physical and psychological distress (4, 41). Teens who experienced cyberbullying were less likely to experience psychosocial distress compared to those who experienced traditional bullying (41, 42). One possible explanation is that people may engage in cyberbullying both as perpetrators and victims, as well as using aggressive behavior

as a coping or defense mechanism (43-45). Teenagers who had good self-control also displayed greater resilience and less distress against traditional bullying and cyberbullying (46). Furthermore, if victimization occurs in the virtual world, it might not always result in emotional distress (47). Given the distinctive features of online environments, it would make sense that obese or overweight victims could receive support from social media users, which could offset critical remarks from their peers during instances of weight-based cyberbullying (28, 48). An empathic audience might, for instance, oppose (rather than conforming to) the negative content that might be accompanied by the distress caused by others if it is directed at a teenager who receives a derogatory message or image about them being overweight. However, it cannot be stated that the children in the sample are "pure" victims (49, 50). Online bullying victims have the option to act aggressively toward their online bullies in order to enrage them, because physical dominance is often irrelevant in such interactions (50). Anderson et al. (51) examined cyberbullying and the reaction to it on Facebook and found that oppositional behavior in cases of weight-based cyberbullying can encourage onlookers to verbally support the victim. This result extends earlier research on the usefulness of oppositional behavior as a social form on the internet (3, 52-55). This study's evidence for the opposite effect has been proposed as a template for initiatives to prevent cyberbullying (56). Challenging the bully or supporting the victim has been defined as dissenting behavior by Anderson et al. (51). Men showing dissenting behavior were seen to make the most complimentary remarks and had the least negative impressions toward the victims. Bystanders who remained silent expressed more sympathy for the victim, and thought the victim was more "favorable" and "healthier" than those who made insulting comments. This indicates that while some passive bystanders appeared to disagree with the bullying, they did nothing to intervene or support the victim. Future interventions using dissenting viewpoint models for relational and verbal bullying may be more successful for all genders (51, 57). Another study by Marco and Tormo-Irun (58) examined the relationship between cyberbullying and eating disorders in adolescents. The study showed that cyber victimization correlated negatively with body image. Since body shape, size, and weight are the main targets of cyberbullying, insults and negative comments may lead to the development of negative body image in adolescents (59, 60). Additionally, eating disorders such as bulimia, binge eating disorder, or avoidant restrictive food intake disorder were positively correlated with cyber victimization (61). Understanding the effects of both offline and online victimization will help develop treatments for victims, given that adolescent obesity is linked to an increased risk of bullying victimization (45, 61, 62).

CONCLUSION

Cyberbullying is a deliberate, repetitive, and damaging behavior for individuals or groups using communication technologies. Easy access to the target individual, the anonymity of the cyberbully, and the lack of concepts such as time, space, and physical strength cause the number of cyberbullying victims to be higher than traditional bullying. The age group in which the relationship between body esteem and weight is most prominent is adolescents. Being overweight can decrease self-esteem, while increasing depression and suicidal thoughts in adolescents. Cyberbullying can be more dangerous than traditional bullying, and the relevant problems faced by obese individuals may increase in the near future. Obese individuals are more prone to be exposed to cyberbullying during school years and in adulthood. Obese girls are victims of bullying at a significantly higher rate than obese boys. Boys become victims when they are physically weak. Girls bully based on looks and lack of close friends, while boys bully using verbal and physical assault. Victims of online bullying are able to act aggressively toward their online bullies to enrage them because physical dominance is often irrelevant in such interactions. Various options such as social and professional help and support groups may prevent the damage to self-esteem in overweight and obese groups. Internet addiction and cyberbullying can be prevented by conscious internet use, informing children and adults, and parents monitoring their children's internet use during childhood and adolescence.

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REVIEW

THE EFFICACY OF PARTIAL EXCHANGE TRANSFUSION IN NEONATAL POLYCYTHEMIA

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ABSTRACT

Polycythemia is defined as a central venous hematocrit level of more than 65%. Polycythemia occurs because of increased red cell mass, with decreased, normal, or increased plasma volume. On the other hand, hyperviscosity of blood results in increased resistance to blood flow and decreased oxygen delivery. Both polycythemia and hyperviscosity can cause central nervous system dysfunction, hypoglycemia, impaired renal function, and cardiorespiratory distress. Hyperviscosity has also been reported to be associated with long-term neurodevelopmental disorders in childhood. Polycythemia and hyperviscosity are related to alterations in organ perfusion. There is a decrease in end-organ blood perfusion due to changes in red cell mass, arterial oxygen content, and/or viscosity. There are two main treatment approaches to neonatal polycythemia. The first approach is restrictive management, whereas the second approach is partial exchange transfusion, a more controversial one. Partial exchange transfusion is a procedure in which the blood of the infant is diluted. Various studies have had outcomes suggesting no clinically significant short and long-term benefits of the partial exchange transfusion, especially in asymptomatic infants and infants with minor symptoms. However, it is crucial to note that there are no long-term follow-up studies to evaluate the neurodevelopmental status of infants with neonatal polycythemia. In contrast to partial exchange transfusion, restrictive management has been confronted with several difficulties. Therefore, further controlled studies with new methods are needed to observe the long-term effects. In this review, it is aimed to evaluate the efficacy of current and recently retrieved treatment approaches in neonatal polycythemia.

Keywords: Exchange transfusion, hyperviscosity, neonatal polycythemia, newborn, NIRS

INTRODUCTION

Neonatal polycythemia is a condition that has been studied for years to understand neonatal mortality and morbidity due to its assured adverse effects such as delay in neurodevelopment and organ dysfunction yielding renal failure with uncertain treatment success (1, 2). It is characterized by a central venous hematocrit (HCT) level of more than 65%. This threshold was set based on the observation of the exponential increase of blood viscosity after a HCT level of 65% (3). HCT level varies based on the location of blood samplings such as an umbilical vein, peripheral vein, or capillary blood, the age of the newborn at the time of assessment, and the method of processing the blood. In different settings, polycythemia and hyperviscosity are used interchangeably. Polycythemia occurs due to increased red blood cell mass with varying plasma volumes (4). On the other hand, hyperviscosity of the blood leads to increased resistance to blood flow and decreased tissue oxygenation due to decreased delivery. Hyperviscosity can induce organ dysfunction such as central nervous system dysfunction, hypoglycemia, impaired renal function, and cardiorespiratory symptoms (5). Furthermore, it predisposes to stasis in microcirculation, which may result in further hematological disorders (6). Hyperviscosity has also been attributed to long-term neurodevelopmental disorders in children (7, 8). Thus, this review aims to evaluate the efficacy of current and recently retrieved treatment approaches in neonatal polycythemia.

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Incidence

It occurs in 0.4% to 5% of normal weight infants but may rise to 15% in infants small for gestational age (SGA) and 20% in infants large for gestational age (LGA) (9-15). It is less likely in preterm infants with a gestational age under 34 weeks (6, 16). Furthermore, neonates from twin pregnancies are considered to retain a higher risk of polycythemia (17). It is also previously stated that four percent of neonatal polycythemia cases are associated with trisomy 21. A similar observation is noted for the infants with trisomy 21, as neonatal polycythemia is one of the most common hematological abnormalities. High cord blood erythropoietin concentration is assumed to be the reason in affected infants with trisomy 21, which could indicate intrauterine hypoxemia involvement (18, 19).

Risk Factors

It has been mentioned before that preterm infants under 34 weeks are less likely to have polycythemia or hyperviscosity, however, SGA and LGA infants are more prone to have neonatal polycythemia (1). Increased fetal erythropoiesis, red blood cell count, HCT level, and blood viscosity may arise from fetal hypoxia. Chronic fetal hypoxia can be driven by fetal and maternal factors. Pregnancy-related conditions that may result in chronic fetal hypoxia include fetal hyperthyroidism, pre-eclampsia, maternal diabetes, and maternal smoking. There are some other pregnancy-related risk factors such as milking or delayed clamping of the umbilical cord. Milking the umbilical cord toward the neonate may lead to substantial polycythemia, particularly if the newborn is being kept below the level of the placenta (20). Another randomized controlled research has confirmed that late cord clamping instead of early cord clamping (<30 seconds) results in increased HCT levels in both preterm and term newborns (21). However, the benefits of late cord clamping in infant health have been clearly shown and far outweigh the theoretical risk of polycythemia (22, 23). Organ dysfunction as a result of polycythemia and hyperviscosity is related to changes in perfusion. End-organ blood perfusion is reduced because of the abnormalities in red blood cell mass, arterial oxygen content (CaO_2), and/or viscosity (2). Interestingly, clinical signs and symptoms of hyperviscosity may impair the crucial maternal-infant bonding in the first hours of life (24).

Treatment

There are two main approaches for the treatment of neonatal polycythemia. The first approach is restrictive management via hydration and fluid supplementation, keeping the infant warm, nutritional management, and cardiorespiratory monitorization. While partial exchange transfusion (PET) is preferred in symptomatic infants with polycythemia and asymptomatic infants with HCT levels higher than 70%, restrictive management is more confined to asymptomatic infants. PET is a procedure in which the blood of the infant is diluted. It has been demonstrated to decrease pulmonary hypertension, increase cerebral blood perfusion, and improve hypoglycemia and 83 renal function (2). Yet, there are some controversies over PET. Necrotizing enterocolitis (NEC) is a raised concern as the most pronounced complication of PET (25). However, it is questioned whether NEC is the consequence of blood hyperviscosity or the procedure itself (26). The main objective of PET is to preserve circulatory volume while lowering the HCT level and hyperviscous status. The amount of blood to be exchanged is determined by using the formula below:

Volume to exchange = the total blood volume of baby *x (observed HCT - desired HCT)/observed HCT.

*The total blood volume of a baby is taken as 80-90 mL/kg in term babies and 90-100 mL/kg in preterm babies.

In the systematic review of Ozek et al. (5) about the efficacy of PET in neonatal polycythemia to prevent neurodevelopmental disorders, seven randomized controlled or quasi-randomized clinical trials comparing PET to controls in infants with neonatal polycythemia were reviewed. In one of these clinical trials, the effects of PET in neonates in terms of their neurobehavioral status were investigated (2). They divided the neonates into three groups. Of the two groups with neonatal polycythemia, one received the transfusion treatment. The third one was a healthy control group. They compared the effect of transfusion treatment to non-treatment using the Brazelton Neonatal Behavioral Assessment Scale and Neurological Assessment of Prechtl. The examination was performed at 10 days of age. Although a behavioral discrepancy between the transfusion treatment and the control groups was noted, there was no pronounced neurodevelopmental difference among the three groups. At 8 months of age, the infants were finally examined using a scale that is similar to Griffiths Developmental Score. The results were not significantly different between the affected groups who received either PET or not, including the ones who had been considered abnormal earlier. Furthermore, the children in this study were monitored until they reached school-starting age. Their developmental performance was appropriate when they were last seen, which was at two years of age. The significant aspects of the study were that before this study, hypocalcemia and hypomagnesemia were not taken into consideration in hyperviscous newborns. However, the information on the timing of the transfusion and hyperviscosity status of the non-treatment group might be noted as limitations (2). Goldberg et al. (27) studied symptomatic polycythemic infants, dividing them in two groups as either observation or PET treatment. Infants receiving exchange transfusions subsequently improved, whereas the observation group was slower in terms of neurological improvement up to 3 weeks of life. Nevertheless, at 8 months of age, abnormal neurological and developmental findings were no longer present in either group. Lastly, the study carried out by Black et al. (25) showed that the later neurodevelopmental impairments and/or delays were more likely to be seen in the untreated group at some uncertain time of life. Kumar and Ramji (28) examined the effects of PET in fifty-five asymptomatic polycythemic low birth weight (LBW) babies to modify neonatal morbidity and

mortality. Developmental delays using Denver Developmental Screening Test-II, neurological deficits, tone, and deep tendon reflex abnormalities were evaluated over an 18-month follow-up period. It was concluded that neonatal morbidity in asymptomatic polycythemic LBW babies was low and was not influenced by PET (28). Various studies, aforementioned in this systemic review, have had similar outcomes suggesting no significant short and long-term clinical benefits of PET, especially in asymptomatic infants and symptomatic infants with minor symptoms. Additionally, there might be a risk of NEC due to PET. However, it is crucial to note that there is no long-term follow-up study to perceive the neurodevelopmental status of infants with neonatal polycythemia (16, 29-30). On the other hand, restrictive management has been confronted with several difficulties. The first question about the intervention is the threshold of the HCT level. There is a recent study that divided infants into three groups according to their HCT levels (31). Each group included not only symptomatic but also asymptomatic infants. They applied PET to the symptomatic infants independent of their HCT levels (only more than 65% level), whereas asymptomatic infants received hydration with glucose 10% solution, up to HCT levels of 75%. After a 75% level of HCT, asymptomatic infants also received PET restrictive approach and were not associated with increases in short-term neonatal morbidities. The authors concluded that restricting PET to a higher threshold (>75%) in asymptomatic polycythemic newborns did not raise the risk of early neonatal morbidities (31). In contrast to restrictive management, there is a recent approach that suggests no fluid supplementation at all. It should be noted that such an approach has been reported to be effective when HCT levels are up to 75% in asymptomatic newborns with polycythemia (32). Although randomized studies have been done about treatment and neonatal polycythemia so far, local protocols and regional guidelines are based on whether a patient is asymptomatic or symptomatic, there is no international or universal consensus. In symptomatic patients, PET is preferred at 65% HCT, while in asymptomatic children, monitorization and a conservative approach are recommended at the same level of HCT. Especially in asymptomatic children, the threshold can be considered 70 to 75% of HCT (33-35).

Monitorization of the Effects of PET on the Central Nervous System

In infants with polycythemia, Doppler techniques were utilized to show reduced cerebral blood perfusion in normal ranges after PET (2, 16, 36). In addition, with the use of Doppler ultrasound, one can conclude that increased cerebral arteriolar diameter might explain why some infants with polycythemia become asymptomatic (16). A relatively recent study showed the effects of PET on cerebral oxygenation and peripheral microcirculation in neonates with polycythemia using Near-Infrared Spectroscopy (NIRS) and Sidestream Dark Field (SDF) (37). It was the first study to use NIRS to explore the effects of PET on cerebral oxygenation and microcirculation in neonates with polycythemia. PET caused a considerable increase in cerebral oxygenation and faster microcirculation, as measured by NIRS and SDF techniques, respectively. Despite the limited research and inadequate data on better long-term prognosis in neonates who received PET, increased cerebral oxygenation is a potentially desirable impact in favor of PET. Further research is required to determine the consequences of faster microcirculation following PET in this patient population (36, 37).

CONCLUSION

In clinical settings, a higher HCT threshold (>75%) for asymptomatic infants has been demonstrated to be applicable since it did not indicate an increased risk for early neonatal morbidities (31). However, in asymptomatic newborns with polycythemia, the treatment aspects require further study as fluid supplementation may not reduce the need for PET in this population (32). On the other hand, symptomatic newborns with polycythemia can be treated by PET with a favorable outcome (27, 36, 38). There are some morbidities such as hypocalcemia, hypomagnesemia, and respiratory distress attributed to polycythemia and hyperviscosity (2, 5, 39). Thus, in symptomatic newborns, short-term morbidity and mortality rates were decreased with PET treatment (2, 16, 25-30, 38). Yet, there might be some misconceptions, such as the attribution of hypoglycemia to polycythemia, for evaluating neonatal morbidity and mortality (39). Therefore, further controlled studies with new methods, such as NIRS, are needed to observe long-term effects.

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REVIEW

POSSIBLE EFFECTS OF THE ENDOCANNABINOID SYSTEM ON THE PATHOPHYSIOLOGY OF DEPRESSION: MEDICAL TREATMENT APPROACHES BASED ON THIS SYSTEM

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ABSTRACT

World Health Organization sees depression, in other words known as major depressive disorder or clinical depression, as the leading cause of disability worldwide. Interestingly, the mechanism of depression is still not fully clear. Medications used in primary treatment for mood disorders often target the monoaminergic system, however, the low efficacy of these drugs and the increase in the risk of suicide show that other factors might also play a role in the pathophysiology of depression. Therefore, the endocannabinoid system, which has been demonstrated to be strongly associated with depression, has attracted attention. In this review, we aim to discuss the possible role of the endocannabinoid system in the suggested mechanisms of depression and examine the medical treatment approaches that are being developed based on this system to eliminate the adverse effects of current depression medications.

Keywords: Antidepressive agents, depressive disorder, endocannabinoid system

INTRODUCTION

According to the 2021 data from the World Health Organization, approximately 280 million people in the world have depression (1). Nevertheless, it would be wrong to see depression as a psychological disorder that only concerns the person affected. Depression does not only affect the individual psychologically, but people with depression are at a higher risk of cardiovascular diseases, which can be fatal (2). Additionally, suicide, which is perhaps the worst consequence of depression, is the fourth most common cause of death in individuals aged 15-29 (1). Furthermore, if we look at the effects on society, according to a study conducted in the United States in 2021, the national economic burden of depression cases that do not respond to treatment is 43.8 billion dollars (3). Despite treatments such as prescribing antidepressants, electroconvulsive therapy, psychotherapy, and transcranial magnetic therapy, only 30% of patients with major depressive disorder (MDD) experience complete remission or recovery (4). Although the symptoms of depression are attempted to be standardized by the Diagnostic Statistical Manual of Mental Disorders-5 (DSM-5) criteria, they largely vary. MDD is a mental health condition that requires at least five of the nine symptoms defined by DSM-5, including at least one of either anhedonia (loss of interest in pleasurable activities) or depressed mood, lasting for at least two weeks. Other symptoms may include changes in appetite, sleep disturbances, fatigue, difficulty concentrating, and thoughts of death or suicide. The use of *Cannabis sativa*, commonly referred to as marijuana, can be traced back to ancient times. In ancient Chinese cultures, it was used for medicinal purposes, particularly for pain relief. Today, marijuana is used to stimulate appetite in acquired immunodeficiency syndrome-related cachexia, alleviate nausea and vomiting associated with cancer chemotherapy, and for recreational purposes (5). There are over 70 cannabinoids derived from the cannabis plant to

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this day, and they are classified as phytocannabinoids. Three of the most important of these compounds are cannabidiol (CBD), cannabinol, and Δ9-tetrahydrocannabinol (THC), which is the psychoactive component (5). In addition to phytocannabinoids, the cannabinoid group includes naturally produced endocannabinoids [arachidonoyl ethanolamide (AEA) and 2-arachidonoylglycerol (2-AG)] and synthetic cannabinoids (dronabinol, nabilone) (5). Endocannabinoids in the body, unlike other neurotransmitters, are synthesized and stored in vesicles, occurring as "on-demand", and then released retrogradely. Of these endocannabinoids synthesized, AEA is hydrolyzed by the fatty acid amide hydrolase (FAAH), while 2-AG is broken down by monoacylglycerol lipase (MAGL). These three groups of ligands bind to the same G protein-coupled receptors, cannabinoid receptors type 1 (CB1R) and type 2 (CB2R). CB1Rs are generally located in the central nervous system. They are mostly present in brain regions that are mainly responsible for mood, such as the hippocampus, prefrontal cortex, hypothalamus, and basal ganglia (6). This explains why these receptors are targeted in treating depression. On the other hand, the synthesis of CB2Rs takes place in leukocytes, spleen, tonsils, and thymus which are peripheral tissues involved with the immune system, which explains other uses of cannabinoids as anti-inflammatory and immunomodulatory agents, and pain relievers (7). The unmet need for depression treatment encouraged the scientific world to do further research and has raised the question if the endocannabinoid system (ECS) has a promising future in this regard.

Endocannabinoid System

The endocannabinoid system is a complex cell-signaling system that plays crucial roles in various physiological processes, including central nervous system development, synaptic plasticity, and the response to endogenous and environmental insults. It consists of endocannabinoids, cannabinoid receptors (CBRs), and the proteins responsible for the synthesis, transport, and degradation of endocannabinoids. Although the two most studied endocannabinoids are 2-AG and AEA, the mechanism of action is generally defined by 2-AG (8). This is because these two molecules have different properties and concentrations. 2-AG, which has a concentration approximately 1000 times higher in the brain, shows a full agonist effect with moderate-to-low affinity to both CBRs; on the other hand, AEA is a partial agonist with high-affinity to CB1R and almost inactive to CB2R (8).

Endocannabinoids are released from postsynaptic neurons in response to the intracellular Ca+2 increase and/or activated Gq/11-coupled receptors, by the mechanisms mentioned above, act as retrograde messengers, and stimulate presynaptic CB1R (9). CB1R and CB2R principally bind to the inhibitory subtype of the G protein; in this way, they may inhibit adenylyl cyclase and voltage-sensitive calcium channels, induce the mitogen-activated protein kinase, and inwardly rectify potassium channels (10). As a result of the various mechanisms mentioned, it inhibits the release of neurotransmitters such as glutamate, GABA, acetylcholine, and serotonin (10). It is mainly CB1 (CB1R) that regulates neurotransmitter release and is primarily located at the presynaptic end of GABAergic interneurons (11). The role of endocannabinoid retrograde signaling in short-term plasticity varies according to the excitation of the presynaptic neuron and the presence of CB1R. The effect of CB1R, stimulated by 2-AG released in response to the postsynaptic Ca+2 increase, is called depolarization-induced suppression of inhibition in the GABAergic afferent and depolarization-induced suppression of excitation in the glutamatergic afferent (9). On the other hand, the effect of 2-AG released by the activation of Gq/11-linked metabotropic glutamate receptors is described as metabotropic-induced suppression of inhibition or metabotropic-induced suppression of excitation according to the cell in which CB1R is located (9). Shortly thereafter, it was shown that retrograde signaling is also responsible for long-term depression (9). Endocannabinoids affect various brain functions such as motor control, cognition, mood, and reward and feeding behaviors by regulating excitatory and inhibitory synaptic release with short-term and long-term effects (12). Therefore, disorders of the ECS are believed to cause many mental disorders, such as depression, schizophrenia, addiction, stress, and anxiety (12).

Prospective role of the endocannabinoid system in depression mechanisms

Despite years of research in the field, the pathophysiology of depression has not been fully elucidated. Our knowledge of the mechanisms of depression and how antidepressants work has been dominated by the monoamine theory of MDD (13). The monoamine hypothesis proposes that depression is caused by the decreased activity of monoamines such as serotonin, dopamine, and norepinephrine in the brain. This hypothesis was developed after the accidental discovery that Iproniazid, a monoamine oxidase inhibitor used against tuberculosis, improved mood by raising monoamine levels at synapses (13, 14). Different antidepressants were later discovered such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin and norepinephrine reuptake inhibitors, yet despite these discoveries, the number of patients who did not respond to treatment suggests that there may be different mechanisms for the disease (13, 14). One system that stands out as a non-monoaminergic depression pathway is the hypothalamic-pituitary-adrenal (HPA) axis in mammals. Corticotropin-releasing hormone is released from the hypothalamus in response to stress, stimulates the secretion of adrenocorticotropic hormone from the pituitary gland, which in turn secretes glucocorticoids from the adrenal gland. Many important data, including large cohort studies conducted in 2009, support the theory that depression may result from HPA axis malfunction (15, 16). It is suggested that ECS's major function is to reduce the HPA axis' response to stress, and to promote proper stress recovery (17). These results support rodent data showing that ECS activation has an antidepressant phenotype. In contrast, inhibition often has

a pro-depressive phenotype, and they support the theory that ECS interacts with depression via suppressing the HPA axis (17). Genetics are known to play a role in MDD, but it has been a common hypothesis that variations in certain genes may have greater contributions. Genetic research on the *CB1* gene (CNR1) in humans has looked at single nucleotide polymorphisms connected to depressive symptoms and responsiveness to antidepressants. For instance, the clinical response to SSRIs appears to be indirectly influenced by CNR1 (18). Studies have shown that CNR1 variants are associated with resistance to antidepressant treatments and the occurrence of MDD (19, 20). However, there are also studies that claim the opposite: Juhasz et al. (21) found that the *CNR1* gene is associated with high neuroticism and low agreeableness and interacts with recent negative life events to predict current depressive symptoms. On the other hand, Hillard and Liu (22) argued that endocannabinoid signaling plays a role in the etiology and treatment of major depressive illness and that the *CNR1* gene may be a potential target for new antidepressant therapies. Despite conflicting evidence, research of the role of the *CNR1* gene in MDD is ongoing. Another mechanism that is thought to be related to depression is neurogenesis. Many preclinical and human studies have revealed that MDD is linked to decreased brain-derived neurotrophic factor (BDNF) activity, induced apoptosis, and decreased neurogenesis in certain parts of the brain (23-25). Besides that, clinical investigations show that MDD patients receiving long-term antidepressant maintenance therapy, do not display the hippocampus atrophy seen in those not taking medication, and successful antidepressant treatments have been shown to induce hippocampal neurogenesis and increased BDNF (26, 27). Considering how the ECS affects the proliferation and differentiation of hippocampal cells, we can conclude that CB1 signaling plays a significant role in promoting neurogenesis. When adult rats were used as model organisms, long-term administration of the CB1 agonist HU210 increased neurogenesis in the hippocampus, and induced behavior resembling that of an antidepressant during the forced swimming test (28). This finding suggests that the enhancement of hippocampus neurogenesis is responsible for the antidepressant-like effects produced by the CB1R agonist (29). As for the relationship between MDD and neuroinflammation, many studies have revealed that cytokines, hormones, and oxidative stress markers are involved in the pathophysiology of depression (30). For instance, cortisol, a hormone produced by the adrenal gland in response to stress, has been linked to the development of depression (30). Another study supporting this theory showed that patients with major depression had higher average levels of interleukin-6 and C-reactive protein compared to the control group without depression (31). The immunomodulatory properties attributed to CB2R in particular suggest that ECS may affect the neuroinflammatory process in MDD (32). CB2 agonists exert their neuroprotective effects by inhibiting neurotoxic factors and suppressing microglial activation (33). Also, many genetic and pharmacological studies in rodents have supported the effect of CB2R on emotional behavior, including depressive-like behaviors (34). García-Gutiérrez et al. (35) revealed that overexpression of CB2 receptors in mice, reduced depressive-like behaviors in the tail suspension test. In parallel, CB2-Knockout mice that lack CB2 receptors, exacerbates stress-induced neuroinflammatory responses (36).

Promising antidepressant drugs: an approach to the endocannabinoid system

Cannabidiol and THC both affect the ECS, but in clinically different ways. While THC is responsible for users' "high" feelings, early studies have shown that CBD exhibits potential therapeutic effects (37). In connection with this, in this section, we will talk more about CBD, which is a natural negative allosteric modulator of CB1Rs and CB2Rs. It has been noted that CBD possesses neuroprotective and anti-inflammatory properties, though the exact mechanism is unknown (18). An ongoing, unpublished, double-blind, randomized, and placebo-controlled clinical study (NCT03310593) examines CBD's potential to alleviate anxiety and depression in bipolar disorder patients (38). The findings of this will be important in ascertaining whether CBD is a viable option for enhancing the pharmacological therapy of these types of psychiatric patients. Primarily through the activation of 5-HT1A serotonergic receptors, CBD showed antidepressant efficacy in animal models of depression, producing an antidepressant-like effect whether administered alone or in conjunction with sub-effective dosages of the antidepressants fluoxetine or desipramine (39, 40). Studies have shown that these effects of CBD in the animal model vary depending on the strain, gender, age, and the pattern of CBD administration, meaning whether it is acute or chronic (40-44). The chronic unpredictable stress paradigm that mimics depression in laboratory rodents evokes passive coping attitudes such as learned helplessness and anhedonia that meet MDD diagnostic criteria. 26 studies were included in a review and meta-analysis that was published in 2022 and showed that cannabinoid treatment lessened the effects of chronic unpredictable stress on anhedonia, learned helplessness, novelty-suppressed feeding, time in the anxiogenic setting, and entry into the anxiogenic context. However, more research is required to decide whether CBs are an effective long-term treatment for stress-related psychopathologies like depression due to the fact that mice received substantially more benefit from cannabinoid protective effects than rats (45). Numerous synthetic cannabinoids have been created to focus on distinct ECS mechanisms. Enzyme inhibitors for the enzymes FAAH and MAGL are URB597 and JZL184, respectively. To test the role of URB597 on depression the following study was conducted using a common set up of the sucrose preference test. This experiment involves measuring rats' preference of drinking sweetened water or plain water to gauge reward sensitivity over differing levels of URB597. The condition of anhedonia is thought to be reflected in decreased ingestion of pleasant solutions (46). Chronic administration of URB597 exerts antidepressant-like effects such as normalizing body weight gain and sucrose intake in rats

exposed to chronic mild stress. As a result of the drug regimen, AEA levels in the midbrain, striatum, and thalamus increased (47). These findings support earlier studies demonstrating that URB597 improves acute stress-coping in the mouse tail-suspension test and the rat forced swim test (FST) (48, 49). URB597 is thought to be a possible treatment for anxiety and depressive disorders based on *in vitro* and *in vivo* investigations, but clinical trials of URB597 have been put on hold because of severe side effects (18, 50). Rimonabant (SR141716) and AM251 are CB1R antagonists and have inverse agonist effects when administered chronically. These drugs have also been studied as potential targets for depression treatment. A meta-analysis of the randomized trial data revealed that those who received 20 mg of rimonabant for obesity treatment, were 2.5 times more likely to stop taking the medication because of depressive mood disorder than those who received a placebo (51). This medication had to be taken off the market after three years due to the high risk of serious psychiatric disorders, including anxiety and suicidal thoughts (18). Likewise, in other studies, 21 days of intraperitoneal rimonabant (10 mg/kg) treatment raised immobility time in FST and declined sucrose preference (52).

CONCLUSION

Although the monoamine hypothesis is the most emphasized theory in the pathophysiology of MDD, genetic factors, hyperactivation of the HPA-axis, neuroinflammation, and loss of neurogenesis also play a role. This review summarizes the effects of ECS on these theoretical etiologies of MDD. The roles of ECS in etiology suggest that antidepressant effects can be produced through this system, and in most rodent studies, activating the ECS appears to produce antidepressant-like responses in various behavioral tests. Depending on the dosage, mode of administration, and other variables, effects can vary, but in general, direct and indirect activation of ECS components has the potential to be antidepressants. Unfortunately, results in human studies are not compatible with animal models. This is because most studies in humans have examined depression as a secondary condition while addressing a medical disorder other than depression (pain, multiple sclerosis) (46). For instance, a recent meta-analysis yielding 924 records from clinical trials found that there were no studies investigating the efficacy of CBD by assessing depressive symptoms as the primary outcome (53). In conclusion, ECS is thought to play a role in both the development and treatment of MDD, although further research is required to prove this hypothesis.

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REVIEW

THE ROLE OF HOST GENETIC POLYMORPHISMS ON CORONAVIRUS DISEASE 2019 PATHOGENESIS

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ABSTRACT

An agent that emerged with a series of pneumonia cases of unknown etiology in China in December 2019 and caused the coronavirus disease-2019 pandemic, has been defined as severe acute respiratory syndrome coronavirus 2 as a result of studies conducted in a group of patients presenting with cough, dyspnea, and pyrexia. Viral entry into host cells starts and affects critical steps of pathogenesis. This step includes host receptor-viral spike protein interaction and enzyme activity. Varying degrees of host responses to viral entry are observed among individuals. Polymorphisms, that may be detected in communities and attributed to host cells, have a role in the pathogenesis of coronavirus disease infection. The reason why this has been considered is that receptors, enzymes, and other physiological response mechanisms' structures are idiosyncratic. Genetic variants that aid spike 1 protein and angiotensin-converting enzyme 2 binding are associated with susceptibility to infection because it is easier for the viruses to enter cells. On the contrary, genetic variants that inhibit binding are related to better outcomes because it is harder for the virus to invade. The transmembrane protease serine gene is another region for genetic polymorphisms. When there is a genetic variant in the regulatory region two outcomes can occur: up-regulation or down-regulation. Since the transmembrane protease serine gene oversees viral entry, up-regulation or high expression of this gene causes worse outcomes. Specifically, the rs2285666 variant of the *angiotensin-converting enzyme 2* gene is found to decrease expression, making it protective, while the rs12329760 variant of the transmembrane serine protease gene makes patients more susceptible to worse consequences. Many other variants of genes are associated with coronavirus disease, but they require further careful investigation to understand the mechanism behind the relation. Human leukocyte antigen and AB0 blood group genes, vitamin metabolism genes, and others are found to have a role in coronavirus disease pathophysiology. This study aims to show most of the probable polymorphic sites of host cell genetics that may influence the pathogenesis of coronavirus disease.

Keywords: Angiotensin-converting enzyme 2, COVID-19, etiology, genetic polymorphism, SARS-CoV-2

INTRODUCTION

In December 2019, in Wuhan, China, the number of pneumonia cases presenting with cough, high temperature, and dyspnea suddenly increased. The etiologic agent has been identified as the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) as a result of studies conducted on groups of pneumonia patients (1). The coronavirus disease-2019 (COVID-19) pandemic, caused by the SARS-CoV-2 novel virus, was officially declared by the World Health Organization (1). After two and a half years of the outbreak, many vaccines were developed and applied to humans. Various variants of the virus have had different impacts on the public and health systems. The presentation of COVID-19 can vary from being completely asymptomatic to death. Commonly seen symptoms of the infection are pyrexia, dry cough, and fatigue (1). The disease is transmitted via respiratory droplets, mostly due to close contact (2). Studies showed that viral nucleic acid is found in patients' feces, urine, blood, serum, ocular secretions, and semen, however, it is not clear, yet that disease may be transmitted via these routes (2). Also, no information about sexual transmission is present (2). To confirm COVID-19 infection, a real-time quantitative polymerase chain reaction test is extensively used (3). Since the primary system affected by the virus is the respiratory system,

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nasopharyngeal swabs are used to detect viral nucleic acid (3). Non-specific markers of inflammation, such as C-reactive protein and erythrocyte sedimentation rate, are also useful for diagnosis (3). Radiological images show ground glass opacity, which is not pathognomonic of COVID-19 infection (4). Microscopic bilateral diffuse alveolar damage due to loss of both type 1 and type 2 pneumocytes with cellular fibromyxoid infiltrates and interstitial mononuclear inflammatory infiltrates with lymphocyte dominance is seen in patients (3, 4). When cases in China were studied, it showed that the mean incubation period of SARS-CoV-2 is 5-6 days (range 2-14 days) (5). The disease burden is not limited to the death toll and confirmed cases. It is extensively related to the economy, social activities, and education in the world (6, 7). Countries whose economies depend on factors that are affected by the global shock that the pandemic created are more susceptible to indirect losses (e.g., tourism) (8). Direct losses are due to illness and mortality (8). Countries get affected by the virus to different extents, just like individuals. One of the most important differences between individuals is genetics. Everyone has a unique genetic sequence that is inherited from their parents. Individuals might have genetic mutations sporadically (9). Some variants are more common than mutations and they are called polymorphisms (9). It is known that genetic polymorphisms have an important role in the binding of an agent to a host cell, the response of the host cell to the disease, and its susceptibility to the disease (9). This study aims to present the latest data about the effect of detected genetic polymorphisms on COVID-19 infection pathogenesis and prognosis.

Virology

Coronaviruses have four major structural protein-coding genes: Spike protein (S), envelope protein (E), membrane protein (M), and nucleocapsid protein (N) (10). As we know from literature, viral spike protein (S protein) uses the angiotensin-converting enzyme 2 *(ACE2)* receptor in human tissues (3). This makes tissues that have high *ACE2* expression susceptible to viral invasion. Coronaviruses have relatively large (~30 kb), single-stranded, and positive-sense genomes (3). We have encountered a variety of variants since the beginning of the coronavirus pandemic. Since humans are made of the same universal code as viruses, they are at risk to have genetic mutations. While some mutations are functional, some are not. These variants of the virus caused different outcomes, such as worse prognoses and enhanced contagiousness.

Pathogenesis Mechanisms and Possible Polymorphism Sites

Since genetic polymorphisms are alterations in the genetic sequence, structural and functional proteins which are encoded by these altered genes may be linked to overall diagnosis, prognosis, and sequelae of the disease. Not only proteins themselves but also mechanisms that are involved in the infectious process and immune response may be genetically polymorphic. Many sites in the human body are prone to being polymorphic because all levels of functionality are controlled on a genetic basis. When we started collecting data, we were faced with the fact that the most studied polymorphism in the human body is *ACE2* receptor polymorphisms regarding COVID-19 pathogenesis. *ACE2* receptor mutations are studied more in number when compared to other mutations regarding COVID-19 disease prognosis. Virus entry is possible via the *ACE2* receptor for both SARS-CoV-1 and SARS-CoV-2 (11). The virus binds to the *ACE2* receptor with its S protein (1). The S protein has two subunits, each with its distinct function. A complete spike protein consists of a trimer of S1-S2 subunits (12). The S1 subunit binds to the *ACE2* receptor via its receptor-binding domain (RBD), while the S2 subunit helps with the fusion (12, 13). Two processes are crucial for viral entry: binding of S1 to the *ACE2* receptor and S protein priming by host cell Transmembrane Protease Serine 2 *(TMPRSS2)* (14-16). Another process for the virus to enter a cell may be endosomal/lysosomal cysteine proteases cathepsin B and L (*CTSB*, *CTSL*) activity, however, it is not mandatory (14). Several studies stated that furin protease, cellular receptor neuropilin-1, and the *CD147* receptor are involved in SARS-CoV-2 disease infection as well (17-20). The *ACE2* receptor is the main receptor of the Renin-Angiotensin System (RAS) and its expression in cells is regulated by several pro and anti-inflammatory cytokines (21). RAS and opposing systems in the human body regulate the cardiovascular system, blood pressure control mechanism, neural and renal functions (21). *ACE2*, *TMPRSS2*, and *CTSB/L* genes are mostly expressed in kidney, heart, respiratory, gastrointestinal tract tissues, and even blood cells (21). Thus, the symptoms can be seen more readily in these systems and tracts that express the *ACE2* receptor due concentrated viral entry and proliferation (21). Still, tissues that have relatively low expression of the receptor have been affected via indirect mechanisms, such as the immune response of the host (21). The *ACE* receptor is found in healthy respiratory vascular endothelial cells, and therefore, a pathology in those cells may cause elevated serum *ACE* levels, as previous studies showed (22). The *ACE* genotype is considerably polymorphic, however, the extent of thoracic involvement is not found to be significantly related to the *ACE* receptor polymorphisms (22). According to recent studies, new hypotheses are posed for discussion. The relationship between the *ACE2* receptor and hypertensive drugs (*ACE* inhibitors) looks concerning to healthcare providers, and new research studies are being performed. According to the Council on Hypertension of the European Society of Cardiology, people on hypertension medication who use *ACE* inhibitors should continue using their drugs with no changes (23). Viral invasion of vascular endothelial cells, lung cells, and myocytes causes inflammatory changes such as edema, degeneration, and necrosis (3). Cardinal signs of inflammation may be seen. Thus, invasion starts an act on the body via pro-inflammatory cytokines. Interleukins (IL) such as IL-6 and IL-10, tumor necrosis factor (TNF)-α, granulocyte colony-stimulating factor (GCSF), monocyte chemoattractant protein I, macrophage inflammatory protein 1α, programmed cell death protein I, T-cell immunoglobulin, and mucin domain 3 (Tim-3) are the main molecules that have a role in pathogenesis

(24). Increased release of pro-inflammatory cytokines is the etiology of cytokine storm and lymphocyte depletion (25). Degeneration of lungs, myocytes, endothelial cells, cardiac tissue, intestinal lining, and systemic effects experienced by the host are due to these circulating messenger molecules (24). Cardiopulmonary changes may cause a decrease in oxygen saturation, and eventually, cellular damage and cyanosis occur in distal parts of the body. Sensitive but not specific biomarkers are usually elevated, and troponin-T, natriuretic peptides, and IL-6 are prognostic factors related to poor results (3). Cardiac complications such as myocarditis, heart failure, and arrhythmias are among the causes of mortality. Gastrointestinal (GI) system-related symptoms are mainly nausea, vomiting, diarrhea, and abdominal pain (3). Hepatic injury is usually seen, which is detected by elevated enzyme levels of serum alanine aminotransferase, aspartate aminotransferases, bilirubin, and γ-glutamyl transferase (3). Hepatic injury is related to hepatotoxic medication, which can cause systemic inflammation, sepsis, respiratory distress syndrome-induced hypoxia, or multiple organ failure. Another system involved in the pathogenesis of COVID-19 is the nervous system (3). Symptoms are migraine, dizziness, seizure, decreased level of consciousness, acute hemorrhagic necrotizing encephalopathy, agitation, and confusion, accompanied by anosmia, hyposmia, and dysgeusia (3). Two important demographic prognostic factors are sex and age (26). After COVID-19 infection, developing severe complications is more common in men than women (26). As age increases hospitalization increases but not in a directly proportional manner: 0.1% in children and 10% or more in the elderly (26).

Complications of COVID-19 disease may be ordered as laryngeal edema and laryngitis, necrotizing pneumonia caused by a staphylococcal toxin (Panton-Valentine leukocidin), acute pericarditis, ventricular dysfunction, acute myocardial injury, arrhythmias, heart failure, acute respiratory failure, acute respiratory distress syndrome, ventilation-associated pneumonia, sepsis, multiple organ failure, and pulmonary embolism due to acute right-sided heart failure (3). When polymorphisms are studied in COVID-19 infection pathogenesis, it is seen that the *ACE2* receptor, *TMPRSS2*, and HLA are commonly studied polymorphism sites. Viral entry is mediated by the RBD surface network of polar contacts which are Lys417, Gly446, Tyr449, Asn487, Gln493, Gln498, Thr500, Asn501, Gly502, and Tyr505 (27). Variable susceptibility to COVID-19 infection and different outcomes can be explained by age, sex, and race differences between patient groups. When reviews are studied, it is inferred that the A*CE2* and *TMPRSS2* polymorphisms, male sex, and HLA-B*15:03 genotype are more vulnerable to COVID-19 (27). Male sex, old age, and the presence of comorbidities increase vulnerability (27). Both diabetes and hypertension are controlled by the *ACE2* receptor and are the most common comorbidities in COVID-19 patients (28). Because of various conditions, the *ACE2* receptor number decreases over time, and a deficiency of *ACE2* should favor disease progression (28). The *ACE2* receptor gene is located on the X chromosome (29). Males have higher expression of the gene and higher conversion of Angiotensin II than females (30). Therefore, it is concluded that female patients might have lower sensitivity to viral infection (30). In a study, two distinct DNA sequences were found linked to the decreased binding capacity of the S protein to the *ACE2* receptor, thus a favorable outcome and increased resistance to viral entry are reported (31). Also, some specific variants of the *ACE2* gene are found to be a factor in the reduction of expression. The rs2285666 variant of *ACE2* reduces the expression and thus might be protective against viral entry (31). In COVID-19 infection, excessive production of immune mediators causes a cytokine storm. The cells that have a role in the cytokine storm also express the *ACE2* receptor (32). There are many functional variants of the *ACE2* receptor gene that are related to increased binding affinity to the S protein. However, some functional variants are found to be linked to decreased affinity (33). Regulatory variants of the *ACE2* receptor gene increase the expression of the *ACE2* and *TMPRSS2* genes (33). It is found that 13 gene variants increase interaction between S1 and *ACE2*: H378R and S19P, European and African variants, respectively (34). In the same study, some other 18 single nucleotide polymorphisms were found to be related to inhibition of the interaction between S1 and *ACE2*: Q388 L and M82I, American and African variants, respectively (34). An association between the *TMPRSS2* p.Val160Met variant and COVID-19 infectivity has been identified in a study, but this study showed no correlation between increased polymorphism and the severity of disease (35). Another study showed that *TMPRSS2* deficiency reduces the severity of disease (36). Distinct variants were investigated, which showed that variants that highly expressed the gene were more susceptible to disease (36). East Asian populations have a lower frequency of genotypes that are associated with high expression compared with American and European populations (36). Studies revealed that the ABO system of blood groups may have an impact on disease pathogenesis (37-43). In chromosome location 9q34.2, there is a polymorphism known as rs657152 which causes a higher risk of infection for blood group A compared to non-A blood groups and a lower risk of infection for blood group O compared to non-O blood groups (37). A polymorphism (in 19q13.32, rs429358) that alters the gene sequence of Apolipoprotein E causes severe disease in patients with comorbidities such as dementia, diabetes, and cardiovascular disease (38). In the HLA loci, two polymorphisms are found to be associated with disease vulnerability and immunity: B*46:01 and B*15:03, respectively (39). A polymorphism (in the 11p15.5 location, rs12252) found in interferon-induced transmembrane protein 3 (IFITM3) is associated with mild-to-moderate disease (40, 41). Polymorphisms in the TLR7 and TMEM189-UBE2V1 genes were also associated with severe disease (37). Polymorphisms of the Interleukin-6 gene are associated with increased susceptibility to chronic obstructive pulmonary disease, pneumonia, various viral infections, and idiopathic pulmonary fibrosis among different populations via different variants (42). These diseases might present as co-morbidities in COVID-19-infected patients.

Co-morbid diseases also affect the progression and prognosis of the main course of the infection. Some polymorphisms might have an indirect effect, as mentioned above, via increasing the risk of probable co-morbid diseases.

A recent genome-wide association study reported that polymorphisms in the *SLC6A20*, *LZTFL1*, *CCR9*, *FYCO1*, *CXCR6*, and *XCR1* genes were found to be related to severe respiratory failure (43). "Two polymorphisms, the rs11385942 insertion/deletion polymorphism of the leucine zipper transcription factor-like protein 1 (LZTFL1) gene and the rs657152 SNP of the *ABO* gene, are related to severe COVID-19 cases with respiratory failure" (43). The gene responsible for producing methylenetetrahydrofolate reductase *(MTHFR)* is polymorphic among Latinx populations (44). The number of people carrying the MTHFR 677 T-allele is found to be high in this group, as is the mortality from COVID-19 infection (44). Thus, a strong correlation between the C677T variant and mortality from COVID-19 infection was found (44). It is seen that 8 genetic polymorphisms are associated with COVID-19 mortality. These genetic variants were seen on chromosomes 2, 6, 7, 8, 10, 16, and 17 (45). Genes related to ciliary dysfunction (*DNAH7* and *CLUAP1*), cardiovascular diseases (DES and SPEG), thromboembolic disease (*STXBP5*), mitochondrial dysfunction (*TOMM7*), and the innate immune system (WSB1) were found to be related to susceptibility to severe disease (45). *DNAH7* was found to be the most down-regulated gene in COVID-19 infection of bronchial epithelia (45). In a study conducted by Turkish researchers, it was hypothesized that vitamin D binding protein (DBP) polymorphisms might affect COVID-19 infection (46). DBP is known as the most polymorphic protein (46). DBP affects biological functions. Polymorphism of this protein gene is associated with susceptibility to different diseases such as Hepatitis C and metabolic syndrome (46). It was hypothesized that this highly polymorphic gene may be associated with COVID-19 infection. As the result of the study, they found that there is a significant positive "correlation between the prevalence and mortality rates and the GT genotype, while there is a significant negative correlation between the prevalence and mortality rates and the TT genotype at the rs7041 locus among all populations" (China, Japan, Nigeria, Kenya, Mexico, Italy, Türkiye, Finland, Germany, Czech Republic) (46). A relationship is found between the *OAS1* (oligoadenylate synthetase 1) gene variations and Alzheimer's and COVID-19 (47). The single nucleotide polymorphisms rs1131454 (A) and rs4766676 (T) are associated with Alzheimer's disease while rs10735079 (A) and rs6489867 (T) are associated with severe COVID-19 (47). *OAS1* is found to be functional in limiting the pro-inflammatory response of myeloid cells (47). A decrease in *OAS1* gene expression should increase the susceptibility to cytokine storm (47). It is found that the GG genotype of the patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) (*rs738409 locus*) gene is associated with a severe outcome when sex influence is adjusted (27). Also, the same genotype was found linked to being more vulnerable to tissue damage in cases of inflammation and up-regulation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome. However, in the same study, no association between the interferon (IFN) lambda system and the outcome of COVID-19 was detected. Previous studies revealed that the IFN lambda system may be associated with reduced viral clearance in African children with coronavirus and rhinovirus infections (27). In the infection state, the lung parenchyma is extensively infiltrated with macrophages and T helper cells (27). Mer tyrosine kinase (MERTK) is a receptor for macrophage subpopulation M2 (27). In this study, it was found that MERTK polymorphisms do not affect patients in terms of the severity of the outcome (27). Other different studies suggest that the *PNPLA3-rs738409* polymorphism might be protective against severe COVID-19 disease (48-50). Although these studies suggest a protective effect, the *PNPLA3-rs738409* variant has been found to have a higher risk for severe disease, as mentioned earlier (27). Overall, it is difficult to understand how exactly this polymorphism alters disease pathogenesis and further studies are warranted (51).

Study Limitations

The subject of this study is a novel topic that needs further analysis of samples taken from COVID-19-infected patients of different groups in populations. Limited information about DNA polymorphisms causes restricted treatment options. Personalized medicine needs to know the differences among human populations to provide more effective treatment. Experimental clinical studies may obtain more data among world populations to determine which polymorphisms cause severe disease and which do not. Not only for COVID-19 disease but other diseases are thought to be related to genetic variants and heritage. It is incontrovertible to say that most diseases have a genetic background and that severity may be affected by environmental exposures. This study is also devoid of articles that we had to pay for to be able to read. With appropriate funding, more studies can be examined, and more extensive research can be done.

CONCLUSION

Gene polymorphisms and mutations may play a role in disease progression and sequelae. A novel virus, SARS-CoV-2 is one of them. Diseases should be investigated thoroughly to not miss any factors that might contribute to the pathogenesis and prognosis. This is possible via scientiface2 studies. In this study, we aimed to determine whether genetic polymorphisms affect COVID-19 disease pathogenesis and prognosis. It was concluded that genetic polymorphisms among human populations are associated with COVID-19 disease, and they partly determine disease outcome and severity via both direct and indirect mechanisms during the disease state. Most common polymorphisms are attributed to the *ACE2* gene because of its essential role in viral entry mechanisms. Genetic variants that aid the S1 protein and ACE2 binding may be associated with susceptibility to infection because it is easier for viruses to enter cells. On the contrary, genetic variants which inhibit binding are related to better outcomes. The another gene encoding TMPRSS2 is highly polymorphic. When there is a

genetic difference in the regulatory gene region, two outcomes can occur: up-regulation or down-regulation. Since *TMPRSS2* oversees viral entry, up-regulation or high expression of this gene may cause worse outcomes. Other polymorphic sites and variants among ancestry groups and smaller populations need further clinical experimental studies to gather more data for understanding the reality behind disease pathogenesis. One should never dismiss the concept of having comorbidities and underlying causes of the apparent disease state. Nevertheless, while the variant increases the main course of the disease, there might be factors that aid patients in healing.

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REVIEW

ADHD AND ITS EVOLUTION ACROSS THE LIFESPAN

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ABSTRACT

Attention deficit hyperactivity disorder is not only a childhood disorder, but a disorder of childhood-onset. Attention deficit hyperactivity disorder, first described as attention deficit, encompasses a larger spectrum of symptoms that appear not only in children, but also in adults, even in those over 65 years of age. Evaluation of this symptom spectrum is important, as affected adults, especially females, are likely overlooked or misdiagnosed in childhood. They may present later with dire outcomes, such as academic failure, problematic parenting behaviours, workplace problems, risky sexual behaviour leading to miscarriages or sexually transmitted infections, and increased suicide rates due to their vulnerability to depression and anxiety-related symptoms. Structural and biochemical findings were associated with this disorder. Additionally, there are many neuropathological models proposed to explain the nature of attention deficit hyperactivity disorder, such as those proposed by Sergeant and Barkley. Although a lot is known about attention deficit hyperactivity disorder so far, there is still a large lack of information about its prognosis and prevalence in vulnerable or minority populations. In this review, we aim to provide an overview of not only the pathophysiology, but the spectrum of attention deficit hyperactivity disorder symptoms throughout the lifespan with an emphasis on the childhood-onset nature of this disorder.

Keywords: Attention deficit hyperactivity disorder, atomoxetine hydrochloride, neurodevelopmental disorders

INTRODUCTION

"Mental restlessness", a common phenomenon encountered in the modern age, was described in the 18th century by Sir Alexander Crichton. His findings were based on his observations of children who appeared inattentive (1, 2). Almost a century later, in The Lancet, George Still noted that mental restlessness may be caused by both nature and nurture, therefore launching today's most common concept in explaining attention deficit hyperactivity disorder (ADHD) among other psychiatric disorders: An ever-ongoing interplay between the genes and the environment, with the latter encompassing not only inanimate objects but also interpersonal relationships, which was first recognized in the third version of the Diagnostic and Statistical Manual of Mental Disorders (2-4). It is now known that ADHD is not only a disorder of childhood but is better described as a childhood-onset neurodevelopmental condition, emphasizing the spanning nature of this disorder from childhood to adulthood (3). Although the diagnosis of ADHD in children is becoming more common every day, many patients remain undiagnosed until adulthood (3). These patients tend to present in various clinical settings. The most common complaints in ADHD are hyperactivity, inattention, impulsivity, problems in social interaction, and a decrease in academic performance (5). This review aims to provide an overview for a less discussed side of ADHD, its effects on developmental milestones, as ADHD shows high rates of persistence into adulthood. A study conducted by Sibley et al. (6), in 2017 revealed that 60% of children with ADHD had persistent symptoms and 41% of these had impairment due to ADHD also in adulthood. The persistence rates of childhood ADHD into adulthood is also reported to be 20-80% in different studies (7). Caye et al. (8) identified the predictors of persistence into adulthood in the children with ADHD as the following: Comorbid major depressive disorder, comorbid conduct disorder, treatment for ADHD, severe symptoms of ADHD.

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Pathophysiology of ADHD

The intriguing pathophysiology of ADHD can only be examined with the help of different perspectives, ranging from its neurobiology to psychological theories.

Structural changes

Positron-emission tomography studies found out that global cerebral glucose metabolism was 8.1% lower in adults with childhood-onset hyperactivity than in the normally developed control group (9). Significant changes in glucose metabolism were observed in 30 of the 60 specific brain regions (9). The greatest reduction was observed in the premotor cortex (9). The premotor cortex is known to play a role in planning of movements and understanding the actions of others, participating also in the prediction of outcomes of actions and working toward a defined goal (9). Magnetic resonance imaging (MRI) studies showed significantly decreased gray matter, white matter, and brain parenchyma volumes in children with ADHD, with no significant differences in cerebrospinal fluid or myelin volumes (10). Additionally, a reduction in gray matter volume, specific to the right putamen/globus pallidus region, was detected in individuals with ADHD (11). This suggests a dysfunction in frontostriatal circuits, which normally contribute to executive functions (11). Other MRI studies reported volume reductions in frontal lobes and striatum in individuals with ADHD, associating lower tissue volume in these areas with clinical hyperactivity (12). In children with ADHD, clinical symptoms were associated with smaller right caudal anterior cingulate cortex thickness and left-pallidum volume, with the smaller right insular volumes being associated with verbal IQ decrease (13). Functional MRI studies revealed that children with ADHD, when compared to their typically developing (TD) counterparts, have reduced connectivity between the central-dorsal attention networks and default mode network, which play roles in both attention and concentration (14).

Genes and neurobiology

New genetic diagnostic methods allowed researchers to define different loci related to childhood ADHD, which are listed in Online Mendelian Inheritance in Man, and include *ADHD1* on 16p13, *ADHD2* on 17p11, *ADHD3* on 6q12 (15). Additionally, mutations in the *TPH2* gene encoding tryptophan hydroxylase 2 isoenzyme, which is mainly found in the raphe nucleus of the midbrain and plays a role in serotonin synthesis, are not only associated with a susceptibility to ADHD but also with unipolar depression (16, 17). Biederman et al. (18) reported that 28.6% of biologic parents of hyperactive kids had a history of hyperactivity, which raised questions about the complex genetic background of this condition. Monoaminergic neurotransmitters, including serotonergic neurotransmitters, are affected in ADHD. Along with the genes associated with the serotonergic system, coding genes in the dopaminergic system were also found to be involved in the pathophysiology. Some of these genes include *DAT1*, *SLC6A3, DBH, DRD4* and *DRD5* (19-24).

Psychopathology

Although there are many theories that explain the changes in ADHD from a somatic perspective, two main neuropathological models dominate the field, those being "The Inhibition Model" by Barkley (25) presented in 1997 and "the Cognitive-Energetic Model" by Sergeant (26) presented in 2000. Both models are summarized in Table 1. Barkley proposed that the main issue in ADHD is poor response inhibition, which involves three interconnected processes. The chain of processes start with the inhibition of an initial prepotent response upon encountering an event, followed by stopping an ongoing response (25). This allows a delay in the decision to reply, and eventually the controlling of the outer interference leading to distraction (25). The impairment of this circuit ultimately leads to inefficient cognitive performance, including executive functions (25), which in turn results in problems with motor control. If behavioral inhibition is not successful in patients with ADHD, it's likely that a failure in executive functions will appear (25). These executive functions include self-regulation of emotions, motivation, arousal, and some parts of working memory (25). Sergeant describes his "Cognitive-Energetic Model" theory, where ADHD is addressed as a problem of energetic factors that eventually lead to the two hallmarks of the disease: inattention and hyperactivity (26). He also proposed three levels of involvement in the efficient processing of information. These three levels mesh together in various ways. The lowest level includes encoding, searching, decision-making, and motor organization, all of which are parts of computational mechanisms of attention (26). The middle level is composed of energetic pools, including arousal, effort, and activation, which altogether function to respond to stimuli (26). The response process takes place in the arousal phase, and eventually a physical action occurs (27). The upper level is the control center, which is associated with planning, response inhibition, and correction (26). In ADHD, it

Table 1: Examples of neuropathological models to explain ADHD symptoms.

Inhibition Model Barkley (25)	Cognitive-Energetic Model Sergeant (26)
Poor response inhibition during the following three processes:	Three levels in the efficient information procession:
1. Inhibition of a prepotent (immature) response	1. The lowest level: encoding, search, decision making, and motor organization
2. Stopping an ongoing prepotent response	2. The middle level: energetic pools, including arousal, effort, and activation
3. Controlling the outer interference	3. The upper level: control center, associated with planning, response inhibition, and correction
	All three levels could be disrupted in ADHD, leading to different phenotypes.

ADHD: Attention deficit hyperactivity disorder

is not rare to see impairments in all three levels of this model, from motor difficulties resulting from the impairment of the lowest level to the lack of inhibitive response against incoming stimuli in the upper level (26, 27). Additionally, earlier theories suggest an overall increased motivation in hyperactive children, leading to impulsive and uncontrolled performance. These hyperactive children tend to be over-motivated by tangible objects as rewards, suggesting an immature reward-motivation system (28). This leads to worse performance in situations that demand passivity and provide intangible rewards such as verbal acknowledgements or celebrations for special days (28). Non-somatic psychological theories suggest that the primitive reflexes responsible for the survival of the organism in early childhood evolves into a more complicated attention system (29). Overloading this early primitive system may result in alterations in the later more complicated system (29). One of these theories suggests that, selective attentive behavior requires the effortful suppression of other stimuli in order to channel attention to only single focus (29). It was also proposed and later proven that there is a superior system overseeing the target of selective attention (29) This discovery led to the identification of anterior cingulate gyrus as the potential mediator of this ability (29).

Spectrum of Symptoms and Their Variations

The prevalence of ADHD in both adults and children has been reported as 3-5% (30). The latest national survey reported its prevalence in Turkey as 19.5%, with 12.4% of affected individuals having impairments due to this condition (31). The symptoms may change across the lifespan. Younger children are more likely to exhibit externalizing symptoms such as hyperactive-impulsive behavior, while in later childhood inattentive symptoms are more prevalent (32, 33). Fortunately, self-reported suicidality and externalizing symptoms in this age group can be managed via modern ADHD medications (34). It is also important to note that boys tend to present mostly with motor symptoms, which may lead to an increased necessity for professional evaluation during childhood (35). On the other hand, girls present mostly with symptoms of inattentiveness and, as a result, stay clinically "silent" until school age, leading to a gender bias in diagnosis (35). In adulthood, earlier inattention tends to persist, while the hyperactive-impulsive behavior declines and gets replaced by emotional lability, with this symptom even presenting as the main one later in life (35). The gender ratios of newly diagnosed patients also change across the lifespan. 80% of the patients that were diagnosed in psychiatry clinics were males, even though in adult psychiatry, the proportion of males was closer to 50% (35). A gender bias for referral is present and results in a decreased referral rate for females with ADHD for treatment compared to their male counterparts. Gender differences are observed in adolescents, with adolescent girls having lower self-efficacy and problems finding coping strategies (32). They may present depressed or show anxiety-related symptoms more often than their male counterparts, with the male counterparts being more likely to show physical aggression and other externalizing behaviors (32). ADHD is also the most common comorbidity to anxiety in children and odds ratio in anxiety disorders for comorbidity with ADHD was reported to be 3.0 (95% confidence interval 2.1-4.3) (36). Subsequently, one third of children with ADHD have comorbid anxiety disorders. Overlapping symptoms of both conditions may result in underdiagnosis (36). Additionally, incarceration rates are higher in men with ADHD than in women (32). At fertile ages, prevalence of prepartum, postpartum, and climacterium psychiatric disorders, including premenstrual dysphoric disorder, postpartum depression, and overall climacteric symptom scores, were higher in women with ADHD than in controls (37).

ADHD and Addiction

A study conducted in Oslo, Norway, between 2014-2018, observed the prevalences of alcohol use disorder (AUD) and drug use disorder (DUD) in 558 ADHD patients, in 12-month and lifetime periods (38). The lifetime prevalence was 12.0% for AUD and 27.7% for DUD, with men having higher rates when compared to women (38). However, DUD was more than twice as prevalent than AUD in both sexes (38). Lifetime DUD was associated significantly with symptoms of ADHD and emotional dysregulation. However, lifetime AUD did not correlate with either (38). Patients with significant ADHD symptoms were able to reduce their drug use, however, they were less likely to achieve abstinence, although having received the methadone replacement treatment at nine months post-admission (39). Because opiates are commonly abused drugs by individuals with ADHD, current therapies for opiate addiction should be adapted specifically for these individuals since ADHD plays a role in the recovery phase of opiate addiction therapy (39). Opiate abuse may even contribute to the etiology of ADHD. Children of opiate-dependent mothers were more likely to have ADHD than those whose fathers were opiate-dependent (23). This phenomenon was not affected by the fact that the parents had ADHD, suggesting the role of serotonergic and dopaminergic risk alleles (23). Research suggests that ADHD screening should be performed in all patients with substance use disorders because of the common co-occurrence of the conditions (40). The same study also suggests that a detailed substance abuse history should be taken when evaluating patients and that specific information about the status of ADHD-related symptoms in abstinent phases should be acquired. Therapy with stimulants or atomoxetine hydrochloride can be offered for the simultaneous treatment of both conditions (40). ADHD is known to bring about behaviors that contribute to an increased risk of AUD (40). Impulsivity and a malfunctioning award system puts the individuals at risk, therefore, it is common to encounter ADHD in individuals with AUD (40, 41). Addiction to video games is also a common phenomenon, with 23% of all video game players describing their relationship with video games as an addiction (42). In individuals with ADHD, ADHD symptom severity is reported to be positively associated with the severity of their video game addiction, independent from

the type of game played or preferred (42). Smoking mostly accompanies other substance abuse disorders, with 81.4% of all substance abuse patients smoking cigarettes. Similarly, substance abuse patients with ADHD tend to report smoking more cigarettes and having a higher dependency on nicotine compared to non-ADHD patients (43). Patients with ADHD also tend to start smoking earlier in life. The study by Sánchez-García et al. (43) suggested that the comorbid presence of personality disorders with impulsive features may contribute to excessive smoking in individuals with ADHD. The study emphasizes the importance of screening for ADHD in patients with substance use disorders, especially when they present with asocial or borderline personality disorders, where impulse control deficits are prominent (43).

School and ADHD

A 10-year longitudinal study investigating executive function in children with autism spectrum disorder (ASD) and ADHD through its three components (working memory, inhibition, and flexibility) has proven that when compared to their counterparts with ASD, individuals with ADHD showed better improvement in all aspects of executive function, despite never reaching the performance level achieved by TD children (44).

In elementary school children, ADHD can present itself with poor relationships with classmates and poor social preference, resulting in low peer support (45). Children with ADHD tend to have more "non-friends", peers around them with no close friendship ties, and a smaller number of classmates that they share friendship ties with (45). Also, the number of children who are eager to establish friendship ties with their peers with ADHD is small (45). Additionally, the more symptoms a child with ADHD shows, the lonelier he or she is, which in turn leads to exacerbation of ADHD symptoms and peer functioning, further leading to poorer friendship patterns and a negative experience in the classroom (45). Highly symptomatic children were not as good at reading comprehension and decoding written texts when compared with controls (46). Grade one children with ADHD, when symptomatic, tend to have less emotional engagement with school after 3 years, which is partially due to student-teacher conflicts (41). If these conflicts are resolved, increased engagement with school can be achieved as well as increased school performance (47). This was proven by a study conducted in Taiwan where teachers were found to have more knowledge about ADHD than parents and the general public (48). It's important to note that children with ADHD are more likely to be bullied (49). This leads to increased symptom severity, however, no significant relation between bullying behavior and ADHD was established (49). In high school, individuals with ADHD are more likely to repeat years or drop out of school, with females having a higher risk ratio than males (50). On the other hand, participation in after-school activities can lead to a decrease in ADHD symptom severity and eventually less frequent school absences (51). Additionally, when performing writing exercises, students with ADHD tend to write texts of similar length but with less coherence and ideation when compared to TD students (52). They also tend to think less about what they are writing and spend less time reviewing their texts, which results in poorer text quality (52). In college, students with ADHD self-reported higher levels of anxiety and depression, and their parents also reported higher levels of anxiety and depression in their children (53). The levels of anxiety and depression were higher in female patients, showing depressive and anxiety-related symptoms more often (53). Anxiety-related symptoms are more likely to be seen in inattentive type ADHD patients than in combined type patients (53). College students with ADHD are likely to have lower grades, take longer to graduate, and drop out of school. Before and during high school, they report that they are less prepared for college than their counterparts (54). Although it was established that ADHD substantially negatively affects the school performance in every step of the educational system, a treatment of 3 months appears to be helpful in improving school performance; therefore it is crucial to detect the ADHD as early as possible (55).

Work Life and ADHD

Adulthood ADHD is mostly associated with being a "night owl" with only 18.5% describing a preference for early hours (56). The preference for staying up until late hours is associated with inattention and increased impulsive behavior, which might eventually lead to decreased work performance (56). Although individuals with ADHD self-report dissatisfaction when it comes to meeting their own standards and perceived potentials, a lack of performance leading to job loss is less common (57, 58). Employment levels and productivity are reduced in affected individuals, and employment of individuals with ADHD is usually associated with higher costs because of the loss of productivity and frequent work absences (57, 58). Additionally, adults with severe childhood-ADHD, who presented with inattention and comorbid mental disorders, particularly anxiety disorders, are known to be more prone to long-term work disability and occupational impairment (59). An early recognition of ADHD and swift interventions, especially for the inattentive type, is crucial to avoid further impairments in the adult work life. Fundamental workplace interventions and primary care recognition can eventually lead to earlier treatment of the disorder-associated symptoms, not only providing a cost-efficient employee-employer relationship but also an increased overall productivity in the workplace (58, 59). Another suggestion is focusing on ameliorating inattentive symptoms for the treatment of adult ADHD, which can be achieved by combining workplace interventions with pharmacotherapy to promote functioning and to prevent long-term work disability. Addressing ADHD in the workplace can help make use of its positive aspects, such as creative thinking (59). Other ADHD symptoms are less likely to get recognized by co-workers, unless mentioned by the person themselves (60). These may include internal restlessness, difficulty maintaining vigilance, and intolerance of boredom (60). Simulated workplace studies suggest that these symptoms are associated with lower workplace performance in individuals with ADHD (60).

Sexuality and ADHD

There is no significant difference between children with or without ADHD when it comes to the development of sexual characteristics, as proven by Tanner-stage observation through 3 years (61). Sexual development does not seem to be altered with stimulant medication use (61). In adolescence, individuals with ADHD tend to have a higher rate of romantic relationship turnover and a lower rate of physical intimacy, with individuals self-reporting more severe emotional dysregulation tending to engage more in romantic relationships and sexual intercourse as well as unprotected sex (62). In women, the association between emotional dysregulation, impulsivity, oppositional symptoms, and hypersexuality seems to be more prominent than in men. ADHD is more commonly associated with risky sexual behavior (RSB) in women than in men. In women, additionally, ADHD symptomatology has more influence on temper, impulsivity, and oppositional behavior, through its association with RSB; whereas, RSB seen in men with ADHD is only associated with temper (63). Another study conducted on Russian adolescents discovered that being easily distracted and forgetful, along with deficits in planning, is associated with RSB (64). RSB includes history of unprotected sex, increased number of sexual partners, sex under intoxication, and unwanted pregnancies (64). Adolescents with ADHD also are at greater risk of pregnancy, including early pregnancy, which can be alleviated with long-term use of ADHD medications (65). It is important to note that marijuana use potentiates the relationship between RSB and ADHD with conduct problems (66). People with ADHD report more sexual desire and less sexual satisfaction, accompanied by more sexual dysfunction and more masturbation frequency (67). With some studies reporting hypersexual individuals suffering from not only ADHD but also from paraphilias (68). There is not enough data to support a clear relationship between ADHD and paraphilias, although it's known that a high prevalence of ADHD is observed in hypersexual and paraphilic individuals (68). In youth aged 13-22 years, who identify themselves as lesbian, gay, bisexual, transgender, queer, asexual, intersex, or non-cisgender (LGBTQAI +), anxiety disorders, depressive disorders, and post-traumatic stress disorder occur more commonly (69). Data on LGBTQAI + individuals with ADHD and their sexual practices is scarce, although it is known that LGBTQAI + high school students are at an increased risk for illicit drug use (70). It was shown that at risk individuals benefit from socially supportive organizations such as gay-straight alliances, as those in alliances were found to consume illicit drugs less frequently (70). A study on men who have sex with men (MSM) with previous adverse childhood experience revealed that the treatment of a concomitant ADHD may prevent the development of depression in the MSM population (71). It is also important to note that in MSM, hypersexuality is a common feature, primarily associated with emotional reactivity, risk taking, and impulsivity, regardless of the presence of ADHD (72).

Parenting with ADHD

More than 50% of adults with ADHD have at least one child with the same disorder, and approximately 25-50% of the children with ADHD also have a parent with ADHD (73). The parenting behavior can be conceptualized in two dimensions, as proposed Rothbaum and Weiz (74) in 1994 and by Darling and Steinberg (75) in 1993: Effective behavioral control and emotional responsiveness to the child. On the first dimension, the difficulties appear when parents either present insufficient behavior controls or extremely harsh and overreactive parenting behaviors (74, 75). On the emotional responsiveness dimension, an impairment appears as low levels of emotional responsiveness, which can be either expressed as insensitivity to the child's needs, or a distant stance toward the child (74, 75). When a parent with ADHD has self-deficits in working memory, planning, and inhibitory control, this parent will not be able to provide adequate monitoring and clear guidance to his or her children, neither will the parent be able to offer a systematically organized solution to the children's problems. On the other hand, deficits in self-regulation, and therefore the repeating impulsivity of the parent, will likely contribute to the problem, as he or she will not be a proper role model for correct behaviors (73). This situation leads to ineffective parental behavioral control. Parenting stress may eventually lead to hostile or over-reactive discipline, lack of warmth and sensitivity, even rejection by the parent in children, further leading to failure in establishing good emotional responsiveness (73). ADHD-related impairments are also known to affect parenting behavior. According to a meta-analysis of 32 studies, parental ADHD symptoms contributed to harsh parenting behaviors with a variance of 2.9%, to lax parenting behaviors with a variance of 3.2%, and to positive parenting behaviors with a variance of only 0.5%, depending on the child's gender, number of individuals in the family with ADHD, and the method of evaluation (76).

ADHD in Older Population

Although there is still no consensus on how late in life the diagnosis of ADHD is possible, studies about adults over 60 years with ADHD is rare (77). Nevertheless, the diagnostic criteria used in children and young adults can be applied to some extent in older patients (≥50 years), and may correspond to the symptom spectrum in this age group (77). A Dutch study revealed that older adults manifest ADHD symptoms as doing lots of physical activities, sometimes lasting for hours, and having their agendas almost always full, complaining of the shortness of time due to their hobbies or free time activities (78). Some of them also describe themselves as talkative, and some report the existence of an internal restlessness leading to excessive activity, like that of a child (78). It is not rare to observe signs of physical restlessness such as constant head scratching or problems with sitting still (78). Many of the respondents in the study reported restricting themselves from talking a lot, therefore trying to inhibit their verbal impulsivity, as it may result in humorous but also hurtful situations (78). Concentration problems that were encountered in younger ADHD patients seemed to persist in this age group, with difficulty reading a book or official letters, difficulty doing more than one thing simultaneously, or difficulty to concentrate during a boring conversation (78). Low self-esteem, which was

also present in childhood, was rare in this population, however its association with symptom severity is not well-understood (78). The symptom-oriented studies conducted by Guldberg-Kjär et al. (79, 80) in adults aged 65-80 also suggested the persistence of childhood-onset ADHD symptoms even in late adulthood. Additionally, no significant difference was found in levels of quality of life when compared with younger adults with ADHD, however their overall psychological health seems to be better than younger adults with ADHD (81). The age-associated symptom patterns in patients with ADHD is summarized in Table 2.

CONCLUSION

With the latest guidelines emphasizing the childhood-onset nature of ADHD and the increasing effect of cultural differences in the diagnosis, it is important to state that the risk of a gender bias for diagnosis still exists (32). This is especially true for child and adolescent psychiatry, as males are more hyperactive and impulsive, therefore resulting in problems in social environments, and females being more inattentive, leading to decreased school performance (32). When the childhood-onset nature of this condition is taken into account and considering that 80% of diagnosed child and adolescent ADHD patients are male, contrary to only 50% of adult patients, it is important to search for an overlooked childhood-onset ADHD that persists in newly diagnosed female adult patients (26). Adolescence is critical for ADHD patients, as females in these ages mostly have anxiety-related symptoms and depression, which may contribute to suicidality, if combined with other life-threatening psychiatric conditions of this age such as anorexia nervosa or bulimia nervosa (82, 83). It is also important to note that concomitant borderline personality disorder, unlike anorexia and bulimia nervosa, do not significantly contribute to mortality and morbidity (84). For adolescent males, the legal and medical consequences of impulsive actions may result in life-long discomfort (66). Addiction is a serious problem in ADHD and generally a result of impulsive behaviors (38). ADHD is a serious problem in addiction medicine (39). Therefore, not only screening for addiction in patients with ADHD, but also a screening for ADHD in substance abuse patients should be considered, especially when disorders associated with impulsivity such as asocial or borderline personality disorders are present (40, 85). At school age, emotional binding to school through establishing a functioning and constructive teacher-student relationship is required (47). It is also important to note that, children with ADHD are usually the victims of bullying but rarely the bullies themselves (49). In high school and college, psychological support for individuals with ADHD through their problems is of critical importance. These patients have higher drop-out rates, which might result in overall dissatisfaction and feeling of failure (50, 59). The main problem in the work life for ADHD individuals might be widespread working hours, as they tend to stay awake until the late hours. Career counselling to find a fitting career is important, and in the work environment, the education of both employers and employees might raise awareness, therefore contributing to the productivity of individuals with ADHD. Individuals with ADHD a have higher turnover of romantic relationships and lower commitment and physical contact, however, they indulge in risky sexual practices more often (62, 65, 66). There is also a great lack of information about LGBTQIA + individuals with ADHD, a population where other psychiatric conditions are common, including suicidality (69). Lack of appropriate or customary parenting behavior may result in behavioral abnormalities in the children of parents with ADHD. The children of these adults may also lack the role model that they need, as individuals with ADHD are more likely to neglect the needs of their children (33, 64, 73). It is important to keep in mind that older adults with ADHD may still have an overall feeling of boredom or emptiness associated with their condition, and this may contribute to suicidality in the older population, when combined with the common presence of depression (80). To summarize, due to delayed diagnosis in childhood, or due to the possibility that its onset was in adulthood, remembering that ADHD is diagnosable in adults is of utmost importance, especially in patients with psychiatric comorbidities that are hard to manage or resistant to therapeutic options (41, 43, 68). When diagnosing, the care provider should overcome gender bias by proper history taking, especially in younger female individuals with suspected ADHD

Table 2: Phenomena associated with ADHD by age group.

Children	Young adults	Adulthood	Elderly
- Often conflicts with teacher and classmates, leading to low self-esteem - Decreased academic performance (problems with reading comprehension tasks) - Inattention (mostly girls) - Motor hyperactivity, sometimes accompanied by destructive behavior on self or peers (mostly boys) - Addiction to video games - Talkativeness	- Substance abuse - Risky sexual behavior (especially sex under intoxication) - Problems creating emotional or sexual bonds - Small number of friends but a large number of acquaintances - Decreased academic performance (especially in writing tasks) - Anxiety and depression (especially in females) - Addiction to video games	- Harsh or lax parenting behaviors - Stress-management problems - Impulsiveness - Hyper sexuality but less sexual satisfaction - Risky sexual behaviors - Preference for late hours - Inattention - Problems in workplace leading to job loss or inadequate performance - Substance abuse disorders	- Excessive physical activity - Completely full agendas - Shortness of time for hobbies etc. - Talkativeness - Internal and physical restlessness (leading to excessive activities) - Concentration problems (during conversations or reading) - Low self-esteem

ADHD: Attention deficit hyperactivity disorder

(32). In older patients, it should be kept in mind that ADHD can still be a possible diagnosis (77). Finally, it is important to remember that ADHD is a disorder with many features, and it is the duty of the care provider to explore the unseen ones.

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ORIGINAL ARTICLE

EFFECTS OF DIFFERENT RADIATION DOSES ON *ESCHERICHIA COLI*

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ABSTRACT

Aims: The purpose of this study was to investigate the impact of various radiation doses on cellular elements using electron microscopy and to determine if non-irradiated cells in the same environment were also affected. Radiotherapy treatment is widely used for different types of cancers as it can prevent cell division and death through direct and indirect mechanisms.

Methods: To conduct the study, standard strain *Escherichia coli* bacteria were reproduced in six Petri dishes, with one serving as the control. The other dishes were divided into two halves, and increasing radiation doses (2, 3, 6, 10, and 20 Gray) were administered to one side of each dish. Using a transmission electron microscope, the samples were examined, and changes in the cell elements were recorded.

Results: The findings indicated that as the radiation doses increased, the negative effects on the bacteria were more pronounced. In the samples exposed to higher doses of 10 and 20 Gray, the bacteria's integrity was significantly impaired, resulting in a mud-like structure that made the evaluation of cell elements challenging. Furthermore, the non-irradiated area showed similar morphological deteriorations but at a lesser rate.

Conclusion: This study demonstrated the effects of various radiation doses on *Escherichia coli* bacteria and the impact on non-irradiated cells in the same environment, as seen through transmission electron microscopy.

Keywords: Cellular morphology, *Escherichia coli*, quorum sensing, radiation

INTRODUCTION

Radiotherapy is a cancer treatment that can halt cell division and cause cell death through direct and indirect mechanisms. The direct mechanism works by damaging DNA, while the indirect mechanism relies on the action of hydroxyl and superoxide radicals. Furthermore, damage to both tumors and healthy tissues can occur through communication between cells outside the targeted radiation zone. This phenomenon is referred to as the abscopal effect and the bystander effect (1-3). In certain cases, radiotherapy can produce a systemic anti-cancer response, which is known as the abscopal effect. Studies have suggested that radiotherapy-induced DNA damage may activate the immune system, leading to this effect. The abscopal effect is the ability of localized radiation to trigger an anti-tumor response in areas of the body that were not directly targeted by the treatment (4). The bystander effect of radiotherapy, on the other hand, refers to the biological effects of radiation on cells whose nuclei were not directly irradiated. This effect can cause DNA damage, chromosomal instability, mutation, and apoptosis. Bystander signals can also modify the balance between proliferation, apoptosis, quiescence, or differentiation (2). In the present day, immune-oncology is employed to treat cancer patients, and the abscopal effect on cancer cells has been observed in this setting. Furthermore, the bystander effect has been implicated in the development of radiation pneumonia, especially in areas of the lung that have not received radiotherapy (1-5). Cell-to-cell communication is vital for the survival of non-irradiated cells, which can result in non-targeted effects where untreated or uninfected cells exhibit effects induced by signal

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transduction. Tunneling nanotubes are significant in triggering apoptosis in non-targeted cells as a consequence of irradiation (6). Studying the structural and indirect effects of radiotherapy on cells using electron microscopy can be beneficial for medical education and encourage new research. The purpose of this observational study is to investigate the effects of different radiation doses on cell structures through transmission electron microscopy (TEM) and assess any effects on non-irradiated cells in the same environment. We chose to focus on the E. coli strain due to the relatively higher cost associated with preparing cell culture.

MATERIAL AND METHODS

Our study was supported by Eskişehir Osmangazi University Scientific Research Projects Commission with project number 2020-2983. Standard strain *Escherichia coli* bacteria were reproduced at the end of 12-24 hours in the ETUV device in a total of 6 Petri dishes in Eskişehir Osmangazi University Faculty of Medicine, Department of Microbiology. Each Petri dish was divided in half symmetrically with the help of a marker. Then, 2, 3, 6, 10, and 20 Gray (Gy) doses were administered once individually to only one side of each Petri dish surface in Eskişehir Osmangazi University Faculty of Medicine, Department of Radiation Oncology. The irradiation process was done with 6 MV photons from a single field from a 180-degree angle using the Varian Trilogy device, with a 100 cm silver sulfadiazine on the Petri dish surface. The studies required for the examination with electron microscopy were started 24 hours after the irradiation. After all radiation doses, the examination was carried out at the same time, and the examination at different times for different doses was left for future studies due to the limited budget of the study. At the concentrations determined for examination by electron microscopy, the samples were taken from each Petri dish into Falcon tubes. The samples were centrifuged with sodium phosphate buffer at 1000 g for 10 minutes twice, washed, and then taken into 2.5% glutaraldehyde prepared in 0.1 mL sodium phosphate buffer. After 1 night of waiting at +4 °C, the cells were washed with buffer and then placed in 1% osmium tetroxide and were subjected to secondary fixation. Prepared 3% molten agar was added to the cells washed with buffer again and a homogeneous cell-agar mixture was obtained. Small drops of this mixture were instilled onto the slide with the help of a pipette and allowed to freeze. Then, they were divided into small pieces with a razor blade and gently put into brown glass bottles. After block staining with 1% uranyl acetate for 15 minutes, firstly dehydration with gradually increasing alcohol series and then transparency with propylene oxide was performed. Cells taken into Araldite-based embedding material were left to polymerize at 600 °C for 48 hours and were made into blocks. Full thin sections (60 nm) taken with an ultramicrotome (Leica Ultracut R) of the samples were taken on the grit, stained with uranyl acetate-lead citrate, examined in TEM and the findings were recorded.

Statistical Analysis

No statistical comparison method was used in the study since a parametric data evaluation was not performed.

RESULTS

Cellular morphology changes were observed in the cells on the side of the Petri dish, where a radiation dose of 2 Gy was applied. The cell ends took a bottle-shaped appearance, and there were several ghost cells. An atypical morphology was evident, and the cells were emptied. Large-sized hollow structures were formed in the cytoplasm. The cell membranes and the cell walls were damaged, and the apical parts of the cells were melted (Figure 1). On the other hand, it was determined that the damage findings such as the melting of the cytoplasm or change in shape in the cells in the non-irradiated area of the Petri dish were still present, although not at the same extent as the cells in the irradiated area (Figure 2). Ghost cell formation was observed, and their number increased in the part where a radiation dose of 3 Gy was applied (Figure 3). In the non-irradiated area of the Petri dish (Figure 4), vacuole formations were detected with some deterioration in the morphology of some cells, but the ghost cells in this group were negligible compared to the cells of the irradiated group. Significant vacuole formation, electron-dense appearance, lysis, and advanced damage were observed in cells administered at a dose of 6 Gy (Figure 5). In the non-irradiated area of the Petri dish, atypical morphological changes and vacuole formations in the cells, and ghost cells were observed (Figure 6). It was determined that advanced damage findings, atypical cell appearances, vacuole formations, and cell wall and cytoplasm damage occurred in cells that received a 10 Gy radiation dose (Figure 7). Morphological deterioration, electron-dense appearance, and vacuole formation were observed in the cells in the non-irradiated area of the Petri dish (Figure 8). Advanced damage and slight bleb formation were observed in the cells administered at a 20 Gy dose, and morphological deterioration, electron-dense appearance, and lysed cell formations were detected in the cells in the non-irradiated area of the Petri dish (Figures 9 and 10).

DISCUSSION

Radiotherapy treatment leads to cell division and cell death with direct action mechanisms in 20% of cases and indirect action mechanisms in 80%. The indirect effect occurs through superoxide and hydroxyl radicals, while the direct effect is formed by direct DNA damage. As a result of the direct effect, rupture, and breaks occur in the DNA. Therefore, the cell G2 and/or M phases do not proliferate, and cell death occurs. The indirect effect causes ionization and oxidation, which then form hydroxyl radicals as a result. The toxic molecules formed because of free radical reactions cause cell death (6). The cellular responses to irradiation are manifested in several structural and functional changes to cells and cellular organelles. The radiation-induced changes in the cellular and organelle membranes play a significant role in the development of acute

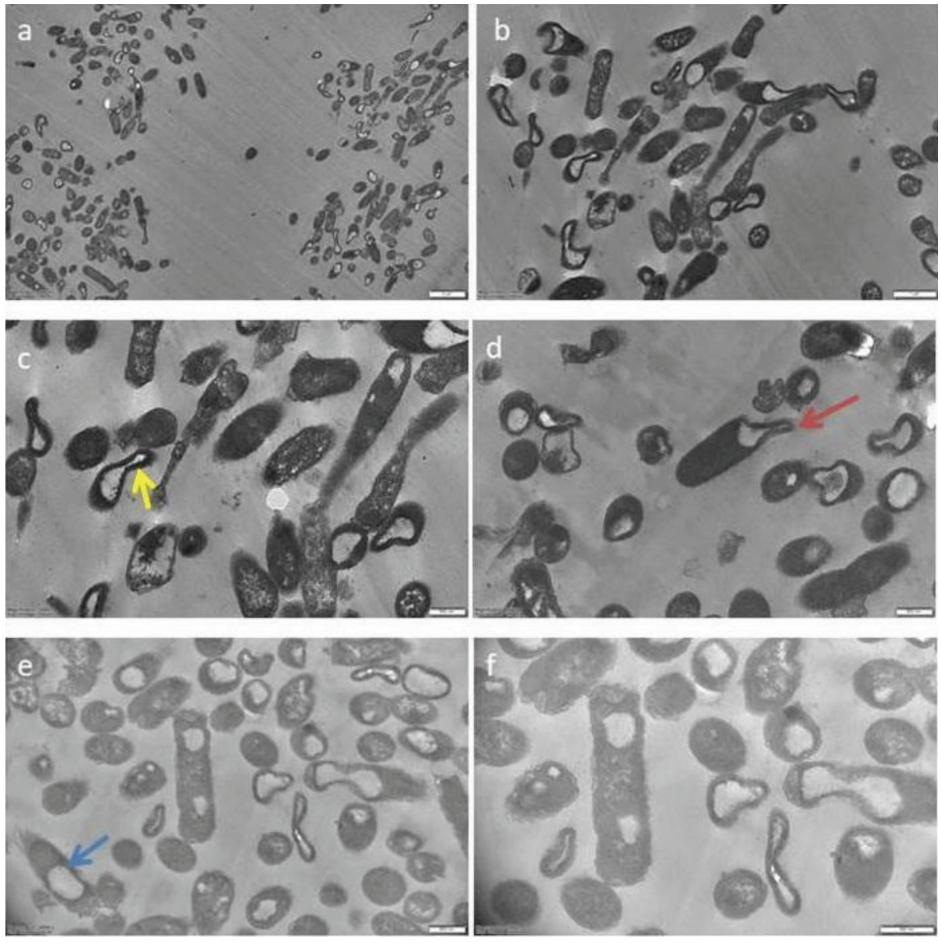

Figure 1: TEM findings of samples taken from the irradiated area of the Petri dish treated with 2 Gy. Yellow arrow: bottle-shaped appearance, blue arrow: large-sized hollow structures in the cytoplasm, red arrow: melted apical parts of the cells, **a:** magnification x5000, **b:** magnification x12000, **c:** magnification x20000, **d:** magnification x20000, **e:** magnification x12000, **f:** magnification x20000.

TEM: Transmission electron microscopy, Gy: Gray

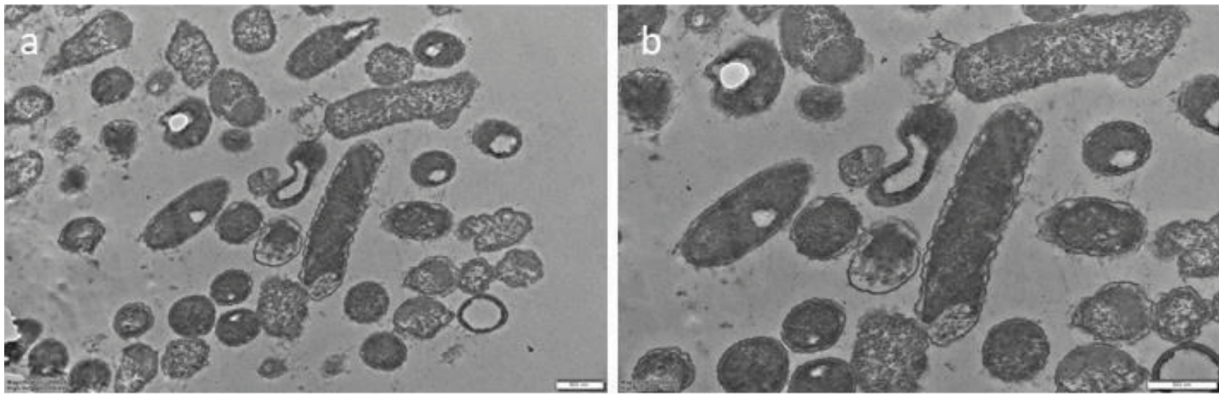

Figure 2: TEM findings of samples taken from the non-irradiated area of the Petri dish treated with 2 Gy, **a:** magnification x20000, **b:** magnification x30000.

TEM: Transmission electron microscopy, Gy: Gray

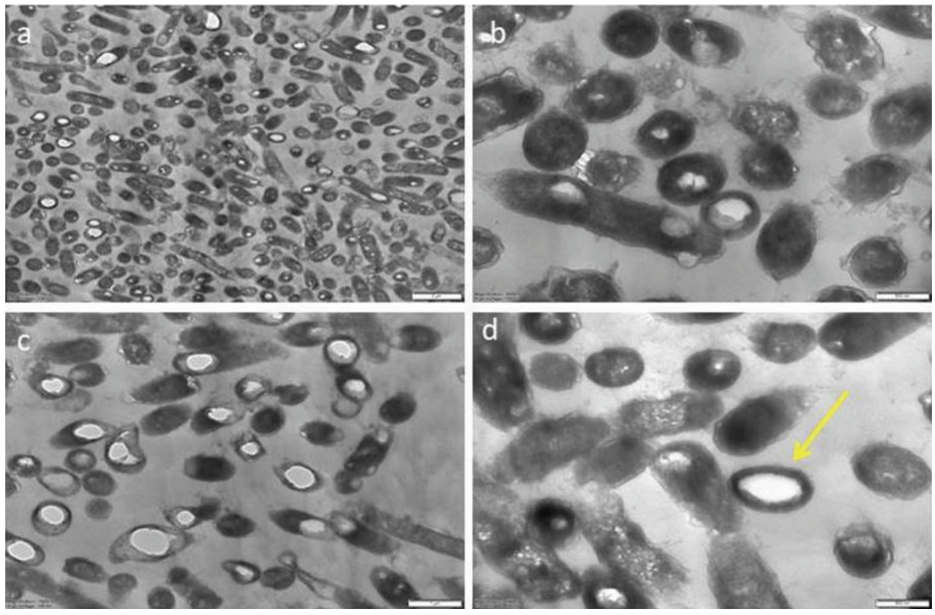

Figure 3: TEM findings of samples taken from the irradiated area of the Petri dish applied 3 Gy. Yellow arrow: ghost cell formation, **a:** magnification x7000, **b:** magnification x30000, **c:** magnification x15000, **d:** magnification x15000.

TEM: Transmission electron microscopy, Gy: Gray

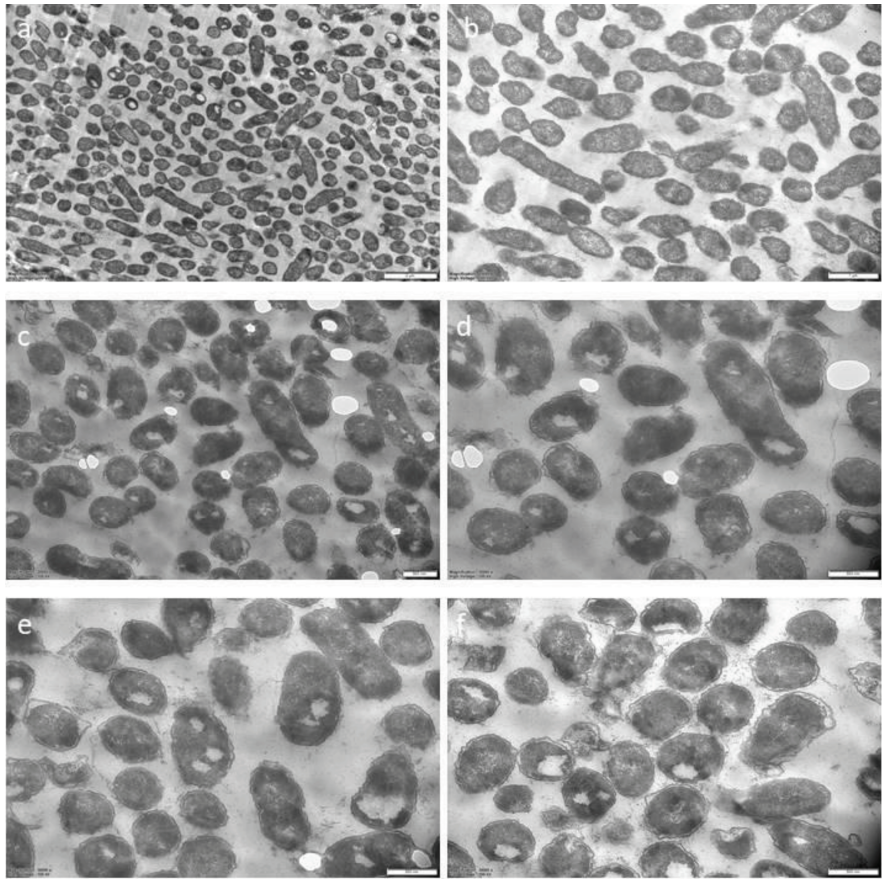

Figure 4: TEM findings of samples taken from the non-irradiated area of the Petri dish treated with 3 Gy, **a:** magnification x8000, **b:** magnification x15000, **c:** magnification x20000, **d:** magnification x30000, **e:** magnification x30000, **f:** magnification x30000.

TEM: Transmission electron microscopy, Gy: Gray

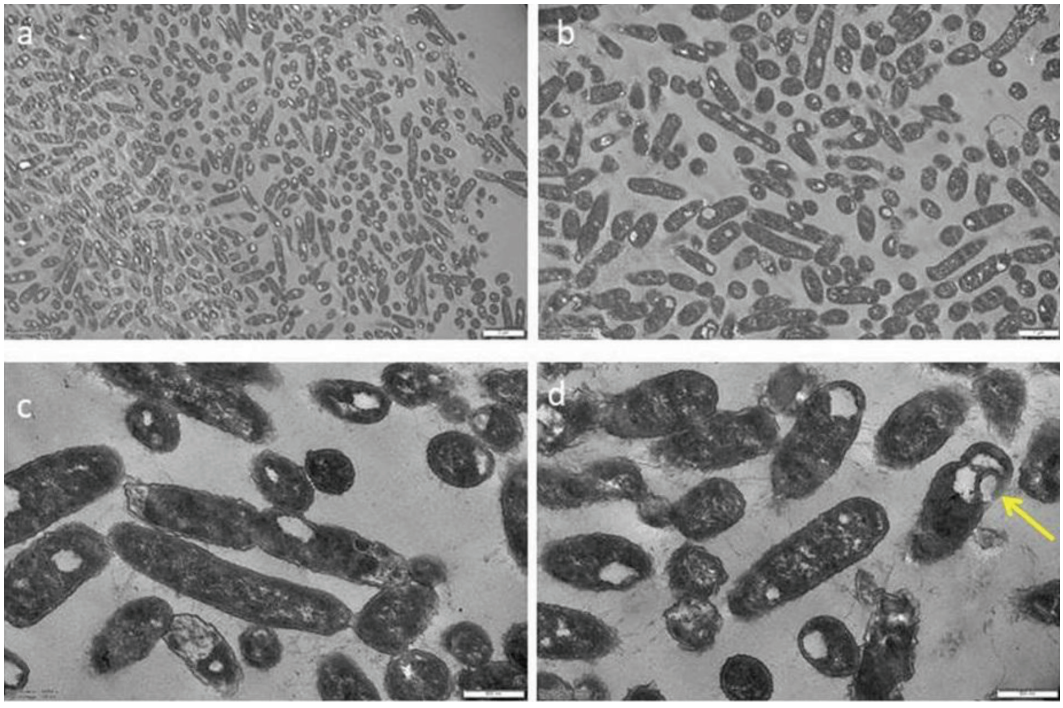

Figure 5: TEM findings of samples taken from the irradiated area of the Petri dish treated with 6 Gy. Yellow arrow: vacuole formation, **a:** magnification x5000, **b:** magnification x10000, **c:** magnification x20000, **d:** magnification x30000.

TEM: Transmission electron microscopy, Gy: Gray

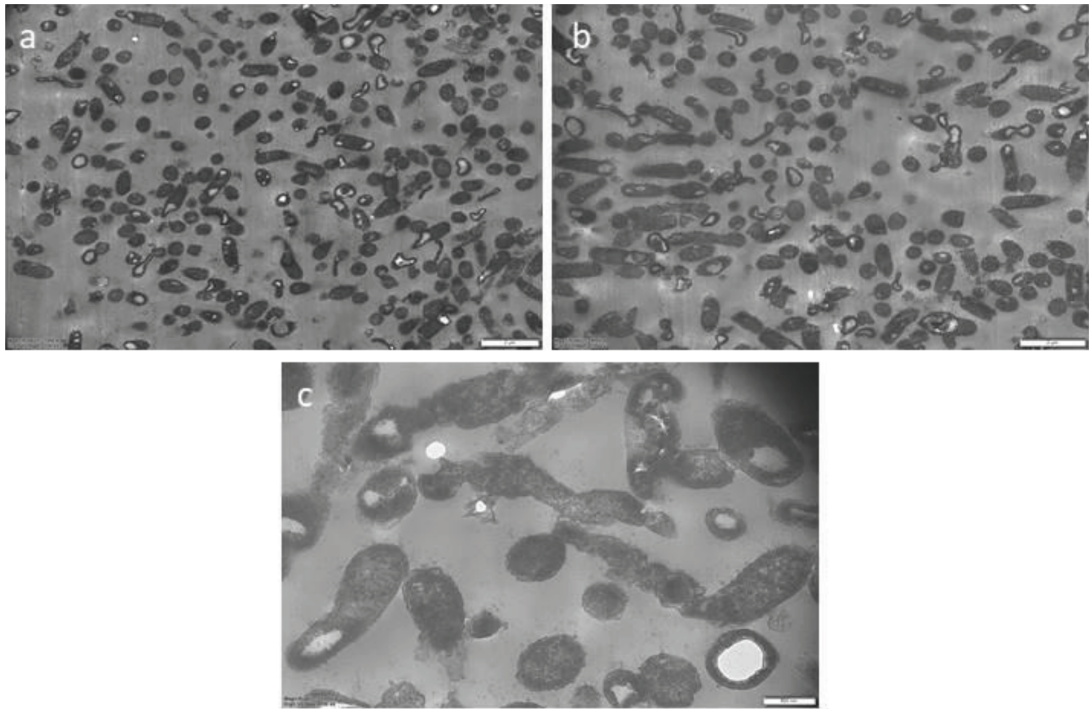

Figure 6: TEM findings of samples taken from the non-irradiated area of the Petri dish treated with 6 Gy, **a:** magnification x7000, **b:** magnification x8000, **c:** magnification x25000.

TEM: Transmission electron microscopy, Gy: Gray

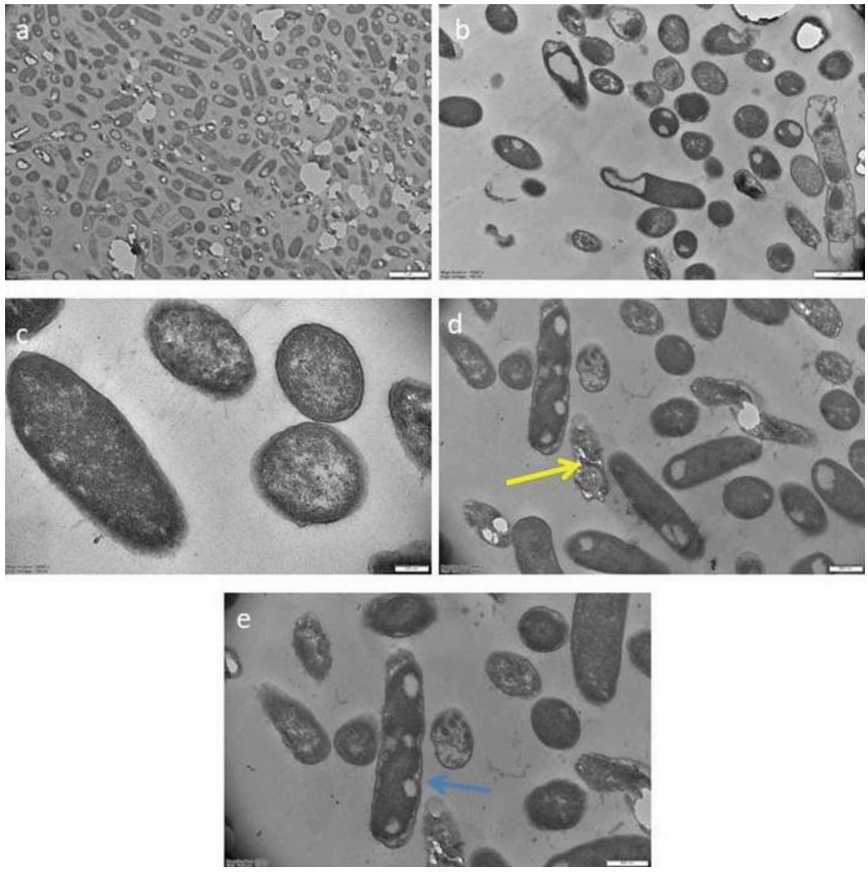

Figure 7: TEM findings of samples taken from the irradiated area of the Petri dish applied 10 Gy. Yellow arrow: atypical cell appearances, blue arrow: vacuole formation, **a:** magnification x6000, **b:** magnification x15000, **c:** magnification x50000, **d:** magnification x20000, **e:** magnification x25000.

TEM: Transmission electron microscopy, Gy: Gray

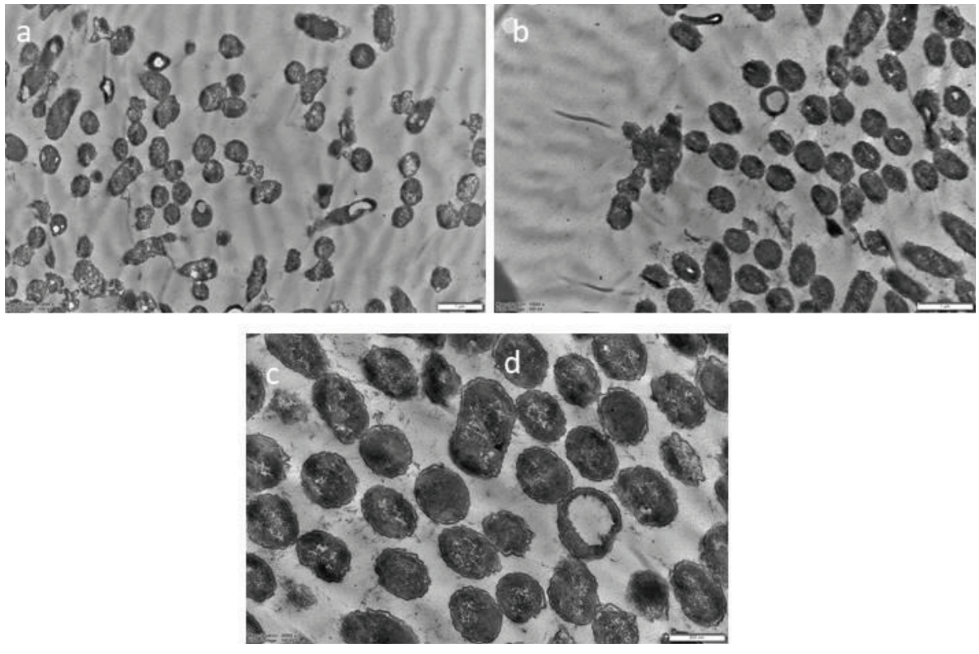

Figure 8: TEM findings of samples taken from the non-irradiated area of the Petri dish treated with 10 Gy, **a:** magnification x12000, **b:** magnification x15000, **c, d:** magnification x30000.

TEM: Transmission electron microscopy, Gy: Gray

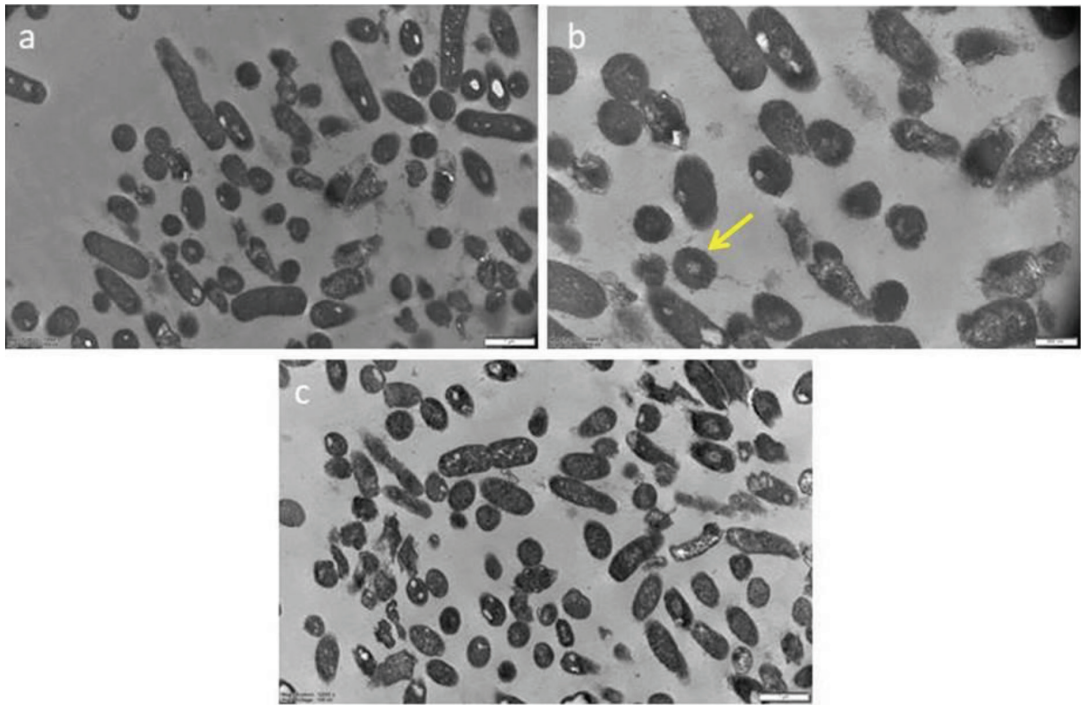

Figure 9: TEM findings of samples taken from the irradiated area of the Petri dish applied 20 Gy. Yellow arrow: bleb formation, **a:** magnification x12000, **b:** magnification x20000, **c:** magnification x12000.

TEM: Transmission electron microscopy, Gy: Gray

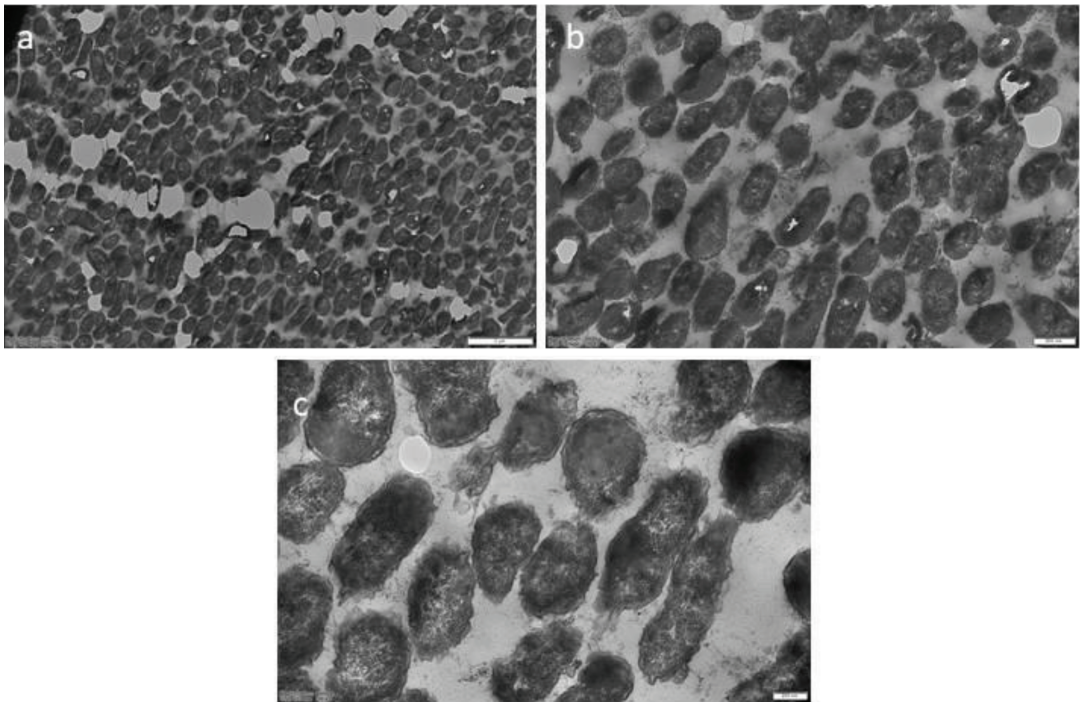

Figure 10: TEM findings of samples taken from the non-irradiated area of the Petri dish treated with 20 Gy, **a:** magnification x8000, **b:** magnification x20000, **c:** magnification x40000.

TEM: Transmission electron microscopy, Gy: Gray

radiation injury. The observed changes in the cell surface and the alteration of intercellular connections are closely related to the reorganization of the cytoskeletal elements in the irradiated cells. The mitochondria, endoplasmic reticulum, Golgi-complex, and the lysosomal system are considered to be direct intracellular targets of irradiation. The radiation effects result as a direct or indirect consequence(s) of absorbed radiation energy. Some data suggest that all these effects are not strictly specific to radiation and may consider general stress responses (7).

The minimum dose we investigated in our study, 2 Gy, is the conventional radiotherapy dose (8). The dose of irradiation may also play a role in determining the type of cell death. Occurred events are dose-dependent in irradiated cells and can be detected after irradiation. Also, it has been shown that the radiation sensitivities of different cell types are also different from each other. In different studies, significant morphological and functional changes in cell elements were often shown at lower doses (7). In this context, the biggest shortcoming of our study is that the effects of low doses were not investigated. The ghost cell is an enlarged eosinophilic epithelial cell with eosinophilic cytoplasm that indicates coagulative necrosis where there is cell death. The ghost cell without a nucleus appears as a shadow cell (9). In our study, we observed that even with low-dose radiotherapy applications such as 2 Gy, disturbances in cellular morphology were initiated, large-sized structures occurred in the cytoplasm where the cell has been discharged, the cell membrane and the cell wall got damaged, and apical parts of the cells melted. It was observed that the number of ghost cells increased with increasing radiation doses. Cell lysis became apparent, and cell damage increased with the application of 6 Gy. After the application of 10 and 20 Gy, bleb formation increased. On the other hand, examination of the samples taken from other Petri dishes except the control dish showed morphological changes similar to the samples taken from the irradiated regions, albeit less than expected. This result was predicted before the examination, and although radiation was applied using a semi-cutter, the samples were taken as far as possible from the region where radiotherapy was applied to prevent the effect of scattered radiation. The two generally accepted basic mechanisms are the bystander effect and the abscopal effect, which describe the radiation effect seen in cells that are not exposed to radiation. The factors released from cells exposed to radiation and the direct communication of cells via junctions cause these two effects (1-3). The bystander effect is the biological effect that appears similar to irradiated cells in neighboring cells that are not directly exposed to radiation. The bystander effect is reported in many cell groups independently of radiation types. The bystander effect can be seen in the γ-radiation that transfers alpha particles and low linear energy. However, there is no clear information about the type of signal that plays a role in both radiation types (1-3). Abscopal effect tries to explain the effects of radiotherapy that occur not only within, but also outside the treatment area. Today, it is generally accepted, and it probably reveals the effects of radiation on the whole body. Similar to the bystander effect, it starts with local DNA damage in irradiated cells or tissues. This can be considered a triggering effect that marks the teleported area as a "stress" field in the body. The remote radiation effect is the release of short and long-distance reporters to transmit stress signals to remote areas through well-preserved inflammatory and immune response networks. Clinically, the most advanced manifestation of this phenomenon is the shrinkage of tumors in remote areas that cannot be reached by irradiation (1-3). It was understood that bacteria could detect the change in the bacteria population and regulate gene expressions via cell-to-cell communications, which was defined as quorum sensing. It has also been reported that bacteria can communicate not only with their own but also across species. This way, bacteria ensure many functions such as spores, gene transfer, conjugation, bioluminescence, biofilm formation, antibiotic resistance, and virulence factors (10, 11).

Limitations

The most important limitation of our study is that the non-radiotherapy area was not checked by dosimetry and the effect of low-dose radiotherapy effects are not investigated. Currently, only the virtual dose information obtained from the treatment planning system has been defined as the non-dose region and no dosimetric measurement has been done.

CONCLUSION

Although it is speculative, the observation of similar morphological distortions, albeit at a lesser rate, in the samples taken from the region where radiotherapy was not applied can be explained by quorum sensing.

Ethics Committee Approval: *N/A*

Informed Consent: *N/A*

Conflict of Interest: *The authors declared no conflict of interest.*

Author Contributions: *Concept: H.A., S.A., M.A.A., S.H., A.Ö., Design: H.A., S.A., M.A.A., S.H., A.Ö., Data collection or processing: H.A., S.A., M.A.A., S.H., Analysis or Interpretation: H.A., S.A., M.A.A., S.H., A.Ö., Literature Search: S.P.K., C.Ç., H.A., S.A., M.A.A., S.H., A.Ö., Writing: S.P.K., C.Ç., A.Ö.*

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ORIGINAL ARTICLE

ATTITUDES TOWARDS GENDER DISCRIMINATION IN MEDICINE AMONG INTERNS AT MARMARA UNIVERSITY FACULTY OF MEDICINE, ISTANBUL, TURKEY

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ABSTRACT

Aims: Gender roles vary from society to society and are subject to change over time. Failure to be gender-sensitive in a physician's professional role and practice can result in negative consequences such as gender discrimination and influence various aspects of medical education, career opportunities, and specialization selection. Gender discrimination can lead to a division in selection of profession and lead to certain jobs being dominated by either men or women. The aim of this study is to reveal the perceptions of intern medical students at Marmara University Pendik Education and Research Hospital about gender inequality and how this issue affects their medical education.

Methods: The present study is cross-sectional in nature. An eleven-item questionnaire adapted from a similar study was applied to determine the opinions of interns regarding gender inequality and discrimination and how this issue has affected their medical education. Out of the 245 interns reached, 150 (62%) agreed to participate in our study. Links to the questionnaire were sent to participants via WhatsApp. Participants remained anonymous throughout the study.

Results: Forty six percent (n=69) of participants were male and 54.0% (n=81) were female. The majority of students wanted to specialize in a surgical field during the beginning of their medical training (53.3%), whereas the most desired branches to specialize in towards the end of medical school were internal branches (52.0%). Interns stated that they encountered sexist behaviors/expressions from their peers, members of faculty, as well as deans (54.67%, 66.0%, and 58.0% respectively) (p=0.169, 0.297 and 0.647 respectively). 39.3% of interns believe that gender equality is not given due importance in medical school (p=0.05). The majority of participants (56.7%) agreed that female interns are more exposed to sexism than male interns (p=0.016). Males are the preferred gender among interns for surgical branches (p=0.01) as well as specialties including invasive procedures (p=0.02). 56.0% of participants agree that a female physicians' profession/specialty plays a major role in her decision to have children later in life (p=0.063).

Conclusion: Gender discrimination is an important issue that affects different aspects of life, including medicine. Gender equality must be promoted throughout medical school; this can be achieved by integrating gender awareness into the curriculum of medical education and providing positive role models and purposeful teaching during internships. Further efforts are needed to cultivate a culture of gender inclusivity throughout this transformative process.

Keywords: Gender in medicine, gender discrimination, gender inequality, medical education, interns

INTRODUCTION

Gender is defined by the World Health Organization as "the characteristics of women, men, girls, and boys that are socially constructed" (1). This definition includes standards and roles lined with being a woman, man, girl, or boy. In the past, many Western societies have subscribed to the notion that women are naturally more nurturing than men (2). One of the ways women were expected to conform to this traditional feminine gender role was by prioritizing their families and working full-time within their homes instead of pursuing jobs outside (2). Other

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attributes associated with femininity include being nurturing, sensitive, supportive, gentle, and sweet (2). On the contrary, men were traditionally viewed as natural leaders within their households (3). As per the traditional masculine gender role, men were expected to provide for their families financially and make important decisions (3). Other characteristics linked to masculinity include dominance, aggression, competition, invulnerability, and risk-taking (3). Gender roles vary from society to society as well as culture to culture and are subject to change over time (1). Gender discrimination is when individuals are negatively treated because of their gender and as a result, are barred from certain opportunities, resources, and rights (4). Research has uncovered evidence of gender inequality in the workplace, with women falling behind men in terms of salary and career progression (5). Women often receive less favorable work conditions, including lower pay, less autonomy, and limited authority, and are frequently relegated to dead-end jobs, reducing their chances of promotion (5). Additionally, women are less likely to hold positions of authority within their workplaces than men (5). According to Schmitt et al. (6) findings, women were at a disadvantage in almost every economic measure when compared to men. Discrimination based on gender is known to influence health, especially mental health. Occupational stress, depression, discomfort, rage, anxiety, alienation, as well as feelings of vulnerability, have been observed in women who have been discriminated against due to their gender (7). Gender discrimination can lead to a division in a selection of professions and lead to certainjobs being dominated by either men or women (7). In medicine for example; women dominate fields that are more nurturing and supportive in nature such as Obstetrics and Gynecology (83.4%), Allergy and Immunology (73.5%) and Pediatrics (72.1%). Whereas men dominate more physically demanding and competitive fields such as Orthopedic surgery (84.6%), Neurological surgery (82.5%) and Interventional radiology (80.8%) (8). Gender roles reflect societal gender stereotypes and differences, which are shaped by cultural views, belief systems, images, and expectations regarding masculinity and femininity (9-11). Society expects women to prioritize raising children and performing household chores, as well as to show their devotion to their husbands in an obedient, patient, understanding, and affectionate way, while men are expected to provide for their families through physicallydemanding work (9).

Women are expected to follow gendered-stereotypes outside of their homes and in their professional lives as well (9). For instance, occupations such as teaching, secretarial work, and nursing are deemed appropriate for women, while fields like politics, leadership, and management tend to be closed off to them (9,11,12). Medical professionals tend to adhere to traditional gender roles in their work, which can have negative consequencesfor patients (13). For instance, female patients are more likely to be asked about their families than male patients, as doctors believe that family issues are more relevant to women (14). This bias also affects the diagnostic process, with many doctors being hesitant to diagnose women with coronary artery disease, and more likely to label their symptoms as psychosocial (13). On the other hand, men with symptoms of depression are more likely to be diagnosed with burnout syndrome (15). Furthermore, research indicates that female patients tend to receive more diagnoses of nonspecific symptoms and signs than their male counterparts, due to doctors' gender-based perceptions (13). Studies have demonstrated that a lack of gender sensitivity among medical professionals can have severe consequences, including gender discrimination and harassment in medical education, career opportunities, and specialty selection (16). Furthermore, gender-related matters are significantly important in medical education (10). As such, many medical schools have begun incorporating gender awareness into their curricula (10, 12). This study aimed to identify and reveal the perceptions of final-year medical students (interns) at at Marmara University Pendik Education and Research Hospital regarding gender equality and how this issue has affected their education thus far. Various aspects of the relationship between gender and education will be explored in this study.

MATERIAL AND METHODS

This study was approved by the Ethics Committee of Marmara University Faculty of Medicine and the Dean's Office (protocol number: 09.2022.615, dated: 01/04/2022). All subjects participated voluntarily. All participants provided informed consent forms to participate in this study. This study was in adherence to the principles of the Declaration of Helsinki. The present study is cross-sectional and descriptive in nature. An evaluation was made by applying a questionnaire to determine the opinions of senior medical students (interns) at Marmara University Pendik Education and Research Hospital about gender equality and how this issue affects their education. All 245 intern students undergoing education at Marmara University Pendik Education and Research Hospital at the time of the study were given the questionnaire; of which 62% (n=150) responded. The questionnaire was sent as a Google Forms link through WhatsApp to all 245 interns. The names of participants were not recorded, all participants were evaluated anonymously.

The survey's questions are aimed to answer these questions: Which specialties do medical students consider suitable for which gender? What are the views of medical students towards gender roles in the education process? To what extent do faculty, health personnel, and peers positively contribute to promoting gender equality in the education process of interns? Do medical students think that there is gender discrimination in the content of the education program, in its application, and in the structuring of the exams and tests? There are a total of 11 items in the questionnaire. The first seven items are questions collecting socio-demographic information. The remaining 4 items are sets of questions that are tailored to our research questions. The questionnaire was adapted from a study conducted in 2020 titled "Gender in Medical Education in Turkey: The Intern Perspective" and used with the permission of the authors (4). The questionnaire has been attached as a supplementary document (Supplementary File). The

demographic variables of the study were age, marital status, and gender; while the dependent variables were the choice of the specialty of the interns, their exposure to sexist expressions, the effects of gender in medical education, and their attitudes towards gender roles.

Statistical Analysis

A trial version of the Statistical Program for Social Sciences was used for the analysis of the data. Mean and standard deviation were used for continuous variables. Descriptive statistics were used to express the findings of this study. Frequencies and percentages were used to illustrate distribution of findings, mean values were used to show central tendencies, and standard deviations were used to demonstrate variability in findings. The chi-square test was used for comparison. A p-value less than 0.05 was deemed significant.

RESULTS

A total of 150 students participated in our study. 46% (n=69) were male, and 54% (n=81) were female. 98% (n=147) were single, and only 2% (n=3) were married. The mean age of the participants was 24±1. Table 1 shows the fields of specializations that participants wanted to enter at the beginning of medical schoolversus towards the ending of their medical education. When asked the question "Do you think that the concept of gender equality is given due importance during medicaleducation?"; 27.3% of the participants (53.7% male and 46.3% female) agreed, 39.3% of the participants did not agree (44.1% male and 55.9% female), and 33.3% of the participants were undecided (42% male and 48% female) (p=0.05). When asked the question "How did your gender affect your work and education life during your clinical education and internship process?"; 18.7% of the participants (21.6% male and 78.4% female) stated that they were adversely affected, 24.7% of the participants (75% male and 25% female) stated that they were positively affected, 56.6% of the participants (47.1% male and 52.9% female) stated that it did not affect their lives (p<0.05). Table 2 shows the responses to five questions about exposure to sexist expressions and behaviors. It is important tonote that the results of Table 2 were not statistically significant with a p-value greater than 0.05. The interns were asked which gender they preferred in different roles, and the findings are summarized in Figure 1. It is important to note that participants that selected "Gender is of no importance" mean that they do not have a preference for either gender in that particular role - they are neutral. Only the results related to "physician", "role model", "branches with invasive procedures" and "surgical branches" were found to be statistically significant with p-values of 0.025, 0.000, 0.001 and 0.002, respectively. Significant results from Figure 1 were reorganized as Figure 2 for better representation. Overall, 1.33% of participants preferred their physician to be a female, whereas 5.33% preferred their physician to be a male. The remaining participants (93.33%) did not have a preference of gender for their physicians. Interestingly, 0% of male interns prefer females as their physicians, and 10% of male interns prefer males as their physicians (p=0.025). This suggests that there is a statistically significant difference in the preference of the gender of a physician, supporting the hypothesis of an inequality in gender preference in favor of male physicians among interns. Overall, 6.67% of participants preferred their role models to be female, whereas 8.67% preferred their role models to be a male. The remaining participants (84.67%) did not have a preference of gender for their role models.Women are seen as role models by 11% of females and only 1% of men. On the other hand, men were seen as role models by 17% of males and only 1% of females (p<0.001). This indicates that there is a statistically significant difference in the preference of the gender of a role model, supporting the hypothesis of an inequality in gender preference in favor of male role models among interns. Overall, 0.67% of participants preferred females as physicians in branches with invasive procedures, whereas 13.33% preferred males as physicians in branches with invasive procedures. The remaining participants (86.00%) did not have a preference of gender for physicians

Table 1: Students' specialization preferences.

Specialties	Beginning of Medical School (%)	Ending of Medical School (%)
Basic sciences	2.00	4.00
Internal	31.33	52.00
Surgical	53.33	36.00
Undecided	13.33	8.00

Table 2: Exposure to sexist expressions and behavior during interns' medical education.

	Yes (%)	No (%)	Undecided (%)	p-value
I have encountered gendered discourse and behaviors by my peers during my medical education.	54.67	38.67	6.67	0.169
I have encountered gendered discourse and behaviors by members of teaching staff during my medical education.	66.00	29.33	4.67	0.297
I have encountered gendered discourse and behaviors by health personnel during my medical education.	9.33	75.33	15.33	0.270
I have encountered gendered discourse in various situations (presentations, discussions, at the patient bedside, etc.) during my medical education.	50.00	40.67	9.33	0.675
I have encountered gendered discourse and behavior by deans and assistant deans during my medical education.	58.00	36.67	5.33	0.647

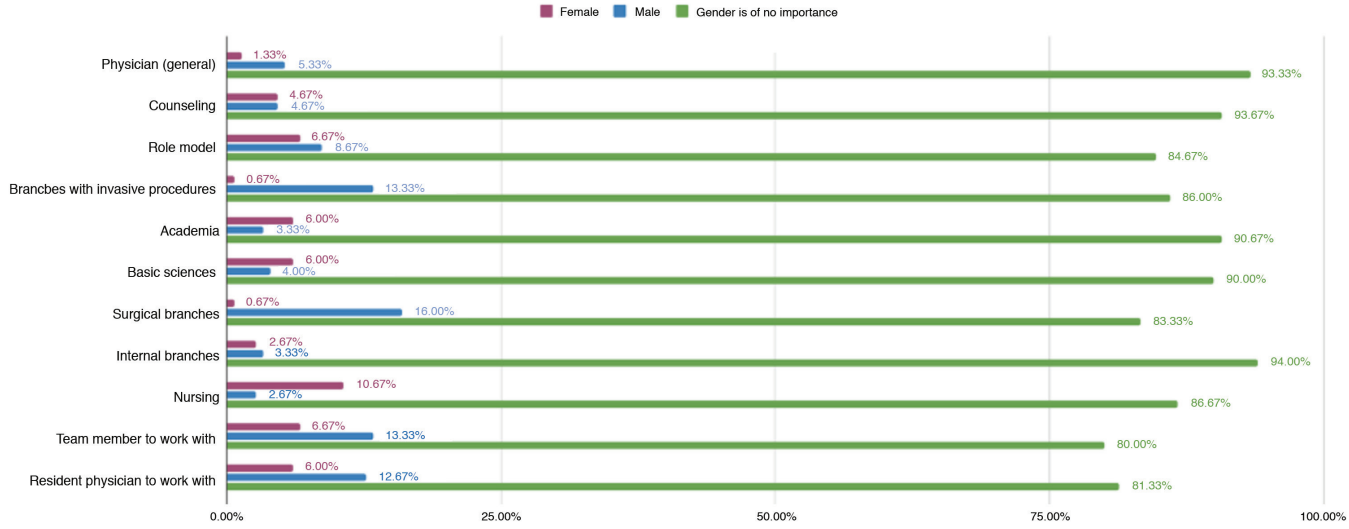

Figure 1: The genders that interns prefer for certain roles in healthcare.

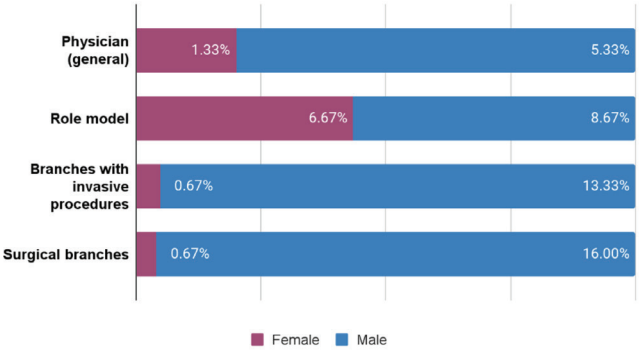

Figure 2: The genders that interns prefer for certain roles in healthcare (significant results).

in branches with invasive procedures. 0.67% of participants preferred females as physicians in surgical branches, whereas 16.00% preferred males as physicians in surgical branches. The remaining participants (83.33%) did not have a preference of gender for physicians in surgical branches. In general, men are preferred over women in branches where invasive procedures are intense (13%) (p=0.001) and in surgical branches (16%) (p=0.002) which means there is a statistically significant difference in the preference of the gender of a surgeon as well as a physician performing invasive procedures, supporting the hypothesis of an inequality in gender preference in favor of male surgeons and physicians among interns. Table 3 shows the answers given to the questions about the effect of gender on a physicians' daily life practicing medicine. Seven out of twenty-one questions were found to have statistically significant answers as indicated in Table 3. Table 4 shows the answers to the questions about the effect of gender concerning medical education on a scale from5 to 1; 5 being "strongly disagree", 4 being "disagree", 3 being "undecided", 2 being "agree" and 1 being "strongly agree". Only one out of the fifteen questions was found to have a statistically significant answer as as indicated in Table 4.

DISCUSSION

The present study deals with gender discrimination in medical education/practice in Türkiye from the perspective of intern doctors. While 78% of the females stated that their gender had a negative impact on their lives during the internship, 75% of the males stated that their gender had a positive impact on their lives during the same period (p<0.001). This suggests that there is a statistically significant difference in the impact of gender on the lives of interns, supporting the hypothesis of an inequality in the impact over the lives of interns in favor of the male gender. This situation is similar in other medical faculties in Türkiye where the same research was conducted (4). The research reveals that doctors face gender-based challenges in their practical lives rather than in their years of education (4). Similar studies on this topic have reported that gender bias is more commonly defined by women (17, 18). We observed that the areas of specialization that many interns thought about when they were beginning the faculty changed as they were approaching the ending of medical school. The percentage of participants that had a field in mind to specialize in increased from 60.66% (when they were beginning medical school) to 91.33% (when they were finishing medical school) (p=0.021). It can be concluded that there is a statistically significant difference in the career choice of interns, supporting the hypothesis that newly beginning medical students have not yet been influenced into a career path by their surroundings yet. Gender did not play a significant role in this change (p=0.645), indicating that factors outside of gender discrimination may play a vital role in determining career choices of medical students. While the percentage of students preferring surgical branches decreased from 53% to 36%, the percentage of students preferring internal branches increased

Table 3: Interns' gender-based perceptions regarding physicians and medicine.

	Female (%)	Male (%)	Both female and male (%)	p-value
.... physicians are subjected to mobbing.	12.67	2.67	84.67	0.043*
.... physicians are polite toward patients.	14.00	6.00	80.00	0.101
.... physicians establish greater emotional bonds with patients.	36.67	1.33	62.00	0.187
.... physicians are more stressed due to workload and family responsibility.	44.00	4.00	52.00	0.001*
.... physicians inspire greater confidence.	5.33	7.33	87.33	0.809
.... physicians earn more money.	0.67	31.33	68.00	0.404
.... physicians are more effective in emergency situations.	0.67	12.67	86.67	0.024*
.... physicians make good managers.	4.00	9.33	86.67	0.007*
.... physicians are harder working.	6.67	9.33	84.00	0.005*
.... take greater care over dress and appearance because of professional anxieties.	54.67	0.67	44.67	0.496
.... are more subjected to occupational violence because of their gender.	39.33	13.33	47.33	0.090
.... physicians are more subjected to disturbing behavior from the opposite sex in their professional lives due to their gender.	76.00	2.00	22.00	0.003*
.... physicians cause greater workforce losses because of their biological and social characteristics (such as military service and giving birth).	42.00	5.33	52.67	0.543
.... physicians are more respected and appreciated by management.	3.33	32.67	64.00	0.033
.... are more successful when their spouses are doctors.	12.67	2.67	84.67	0.927
.... physicians' professions play a role in their decisions to have children.	58.00	2.00	40.00	0.063
.... physicians support their male colleagues more in professional matters.	4.67	29.33	66.00	0.562
.... physicians work in easier fields with fewer shifts.	32.67	2.67	64.67	0.375
Medicine is a branch of science dominated by .... physicians.	3.33	27.33	69.33	0.078
.... physicians can live without occupational anxieties because of their gender	5.33	35.33	59.33	0.036*
I would recommend a .... physician to my patients/relatives	1.33	9.33	89.33	0.132

*p<0.05

from 31% to 52% (p=0.024). There is a statistically significant difference in the preference of internal branches over surgical branches, supporting the hypothesis that surgical branches are generally more difficult in comparison to internal branches. However, gender did not play a significant role in this change (p=0.328), once again showing that perhaps factors besides gender discrimination may play a vital role in determining career choices of medical students. It may mean that other factors such as workload, personal life, and financial situation can have a strong influence on their choiceof specialization. It shows that today's medical students are more aware of what they want as a specialty branch, rather than being influenced by gender discrimination or socially imposed roles when choosing their specialty.

Our research revealed that none of the male interns (0%) preferred females over males as their physician or surgeon. Compared to a study conducted among the general population in Saudi Arabia, it was seen that both genders preferred male physicians in surgical branches (50% of men and 39% of women, General Surgery) (p=0.017) because they believed they were more knowledgeable (19). According to their findings, while female patients preferred to be examined by female physicians (54%, Internal Medicine) (p=0.034), it was observed that male patients did not have a gender preference for their physician (55% in Internal Medicine) (p=0.028) (19). This may reveal that although interns have the experience of working in a hospital setting -where they see both genders asequally talented- they are still affected by societal stereotypes. In our study, interns stated that they were also exposed to gender discrimination during their medical education. More than 50% of the candidates agree that female students are more exposed to sexism than male students. A studyamong fourth-year medical students at public and private medical schools in the United States showed that gender discrimination and sexual harassment were more likely to influence the choice of specialties in female students who had previously reported sexual harassment during their education (20). This highlights that while gender discrimination is an important issue in medical education/practice, it can influence major career-related decisions such as choosing certain specialties in different geographic regions. A study conducted at the Harvard Medical School Department of Health Policy and Management demonstrated that female physicians are more patient-centered, encouraging, and reassuring, communicate better with their patients and spend more time with their patients compared to their male counterparts (21). Interns in our study however stated that both male and female

Table 4: Interns' perceptions concerning medical education.

	Strongly disagree (%)	Disagree (%)	Undecided (%)	Agree (%)	Strongly agree (%)	p-value
My gender had an impact on my choice of entering medical school.	77.33	8.67	10.00	2.00	2.00	0.483
The medical education I have received respects gender equality.	12.00	7.33	28.67	24.00	28.00	0.732
During my internship, the division of labor within the team was made regardless of gender.	8.00	10.00	18.00	16.67	47.33	0.269
During my internship, faculty members or residents preferred to work with male students.	34.67	24.00	20.67	14.00	6.67	0.073
Female interns suffer more from gender discrimination than male interns.	17.33	8.67	17.33	32.67	24.00	0.016*
The gender of a medical student is correlated with being successful on an exam.	60.00	14.00	13.33	6.67	6.00	0.754
Female medical students use their sexuality to pass courses.	62.00	18.00	9.33	6.67	4.00	0.104
During exams, faculty members are egalitarian and do not possess a sexist point of view.	11.33	16.00	22.67	21.33	28.67	0.141
Faculty members working in surgical branches emphasize that surgical branches are more suitable for male students.	16.67	12.00	24.00	28.00	19.33	0.956
The sentence "You can't do it" is said more to female students than to male students.	17.33	10.00	16.67	29.33	26.67	0.532
Faculty administrations want male students to take part in student representation as opposed to female students.	56.67	14.00	17.33	7.33	4.67	0.213
Female faculty members do not like female students.	26.00	24.67	19.33	18.67	11.33	0.624
Medical students benefit from the opportunities of medical education (clinical training, participation in congresses, etc.) without gender discrimination.	10.00	6.67	12.67	20.67	50.00	0.151
It is my belief that there are sexist course materials in our curriculum (presentations, lecturer hand resources, videos, etc.).	50.00	18.67	16.67	8.00	6.67	0.226
In small group educational environments, faculty members are egalitarian and do not demonstrate sexism.	10.67	12.00	22.67	16.00	38.67	0.632

*p<0.05

doctors are reassuring, treat their patients kindly, and establish emotional bonds with their patients (87.3%, 80.6% and 62%, respectively) (p=0.809, p=0.101 and p=0.187, respectively). It is obviousto us that interns in our study believe that the gender of the physician is not important in establishing a healthy doctor-patient relationship. This may mean that a doctor's perspective may differ from that of the general population, while also being based on practical experience with colleagues rather than societal and personal views. Medical textbooks, curricula, and other educational resources often contain gender bias, which can negatively affect individuals' attitudes and decision-making processes (17). This can then influence the career opportunities and expectations of students. According to the study participants, academics may also encourage students to choose certain specialty fields based on their gender (17). Our study sheds light on a crucial issue in medicine that can oftenbe overlooked or ignored. By examining the attitudes of interns at Marmara University Faculty of Medicine towards gender discrimination, our research offers new insights into the nature of this problem in the medical profession. Ourfindings contribute to a growing body of literature that highlights the need for greater awareness and action to address gender discrimination in medical education and practice. Gender awareness must be promoted from an earlyprocess in medical education in order to get ahead of gender discrimination both in medical practice as well as society.This study provides a valuable baseline for future research and interventions aimed at reducing gender discrimination and improving equity and diversity in medicine. Our research underscores the importance of addressing gender discrimination not only for the well-being of medical professionals but also for the quality of patient care and the overall health of society. A limitation of our study was low interest by participants to fill out the questionnaire. The questionnaires were distributed to participants during the last few months of medical school. Thisis a very busy and stressful period for interns as they are preparing for their medical licensing exams as well as arranging graduation arrangements. Many participants did not fill out the questionnaire. Among those that did, we can not be sure if they rushed through the questions. Another limitation of this study is that it was only conducted in a single hospital (Marmara University Pendik Education and Research Hospital). As a result, the results of this studycan not be generalized for a larger population. Finally, it is important to emphasize that our study primarily focuses on the subjective experiences and perceptions of the participants, rather than providing objective measures. We recognize the

inherent subjectivity of the data and the potential limitations associated with relying solely on subjective accounts.

CONCLUSION

Gender discrimination is an important issue that affects different aspects of life, including medicine. Our research has shown that doctors make decisions without considering their gender, rather they make judgments based on the gender of other doctors. When we compare the results of this study with those of others, it is obvious that gender discrimination in medical education/practice is prevalent all across the globe. To prevent gender discrimination in medical practices and society, it is crucial to promote gender awareness from the beginning of the medical educationprocess. This can be achieved by integrating gender awareness into the curriculum of medical education and providing positive role models and purposeful teaching during internships. Further efforts are needed to cultivate aculture of gender inclusivity throughout this transformative process.

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Ethics Committee Approval: *This study was approved by the Ethics Committee of Marmara University Faculty of Medicine and the Dean's Office (protocol number: 09.2022.615, dated: 01/04/2022).*

Informed Consent: *All participants provided informed consent forms to participate in this study.*

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Supplementary File

Questionnaire: Attitudes Towards Gender Discrimination in Medicine Among Interns at Marmara University Faculty of Medicine, Istanbul, Turkey

1. Gender: (select one)
☐ Female ☐ Male

2. Age: .....

3. Marital status: (select one)
☐ Married ☐ Single

4. Did you have a field in mind that you wanted to specialize in before starting medical school? (select one)
☐ No
☐ If yes, which field: .....

5. Do you plan on specializing in any field now that you are finishing medical school? (select one)
☐ No
☐ If yes, which field: .....

6. Do you think that the concept of gender equality is given due importance during medical education? (select one)
☐ No ☐ Yes
☐ Undecided

7. How did your gender affect your work and education life during your clinical education and internship process? (select one)
☐ Positively ☐ Negatively ☐ Undecided

8. This question assesses exposure to sexist expressions and behavior during interns' medical education. Do you agree or disagree with the below statements? (select one per row)

I have encountered gendered discourse and behaviors by my peers during my medical education	Agree	Disagree	Undecided
I have encountered gendered discourse and behaviors by members of teaching staff during my medical education	Agree	Disagree	Undecided
I have encountered gendered discourse and behaviors by health personnel during my medical education	Agree	Disagree	Undecided
I have encountered gendered discourse in various situations (presentations, discussions, at the patient bedside, etc.) during my medical education	Agree	Disagree	Undecided
I have encountered gendered discourse and behavior by deans and assistant deans during my medical education	Agree	Disagree	Undecided

9. This question assesses the genders that interns prefer for certain roles in healthcare. Which gender do you prefer for certain roles in healthcare? (select one per row)

	Female	Male	Gender is of no importance
Physician (general)			
Counseling			
Role model			
Branches with invasive procedures			
Academia			
Basic sciences			
Surgical branches			
Internal branches			
Nursing			
Team member to work with			
Resident physician to work with			

10. This question assesses interns' gender-based perceptions regarding physicians and medicine. Which gender do you think most appropriately fits into the dotted lines? (select one per row)

	Female	Male	Both female and male
….physicians are subjected to mobbing			
….physicians are polite toward patients			
….physicians establish greater emotional bonds with patients			
….physicians are more stressed due to workload and family responsibility			
….physicians inspire greater confidence			
….physicians earn more money			
….physicians are more effective in emergency situations			
….physicians make good managers			
….physicians are harder working			
….take greater care over dress and appearance because of professional anxieties			
….are more subjected to occupational violence because of their gender			
….physicians are more subjected to disturbing behavior from the opposite sex in their professional lives due to their gender			
….physicians cause greater workforce losses because of their biological and social characteristics (such as military service and giving birth)			
….physicians are more respected and appreciated by management			
…. are more successful when their spouses are doctors			
….physicians' professions play a role in their decisions to have children			
….physicians support their male colleagues more in professional matters			
….physicians work in easier fields with fewer shifts			
Medicine is a branch of science dominated by …. physicians			
….physicians can live without occupational anxieties because of their gender			
I would recommend a …. physician to my patients/relatives			

11. This question assesses interns' perceptions concerning medical education. How much do you agree or disagree with the following statements? Select a number from 5 to 1. (Select one per row)

	5	4	3	2	1
My gender had an impact on my choice of entering medical school					
The medical education I have received respects gender equality					
During my internship, the division of labor within the team was made regardless of gender					
During my internship, faculty members or residents preferred to work with male students					
Female interns suffer more from gender discrimination than male interns					
The gender of a medical student is correlated with being successful on an exam					
Female medical students use their sexuality to pass courses					
During exams, faculty members are egalitarian and do not possess a sexist point of view					
Faculty members working in surgical branches emphasize that surgical branches are more suitable for male students					
The sentence "You can't do it" is said more to female students than to male students					
Faculty administrations want male students to take part in student representation as opposed to female students					
Female faculty members do not like female students					
Medical students benefit from the opportunities of medical education (clinical training, participation in congresses etc.) without gender discrimination					
It is my belief that there are sexist course materials in our curriculum (presentations, lecturer hand resources, videos etc.)					
In small group educational environments, faculty members are egalitarian and do not demonstrate sexism					
5 = "strongly disagree" 4 = "disagree", 3 = "undecided" 2 = "agree" and 1 = "strongly agree"					

This is the end of the questionnaire. Thank you for your time.

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ORIGINAL ARTICLE

INVESTIGATING THE PREVALENCE OF AUTOIMMUNE DISEASES IN ENDOMETRIOSIS PATIENTS

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ABSTRACT

Aims: This study aims to determine the prevalence of autoimmune diseases in women with endometriosis who were admitted to the Department of Gynecology and Obstetrics, Trakya University Hospital.

Methods: The comorbid autoimmune diseases of 231 women older than 18 years diagnosed with endometriosis by surgery and pathology were examined. Considered autoimmune diseases were: Systemic lupus erythematosus, inflammatory bowel disease (Crohn's disease and ulcerative colitis), autoimmune thyroiditis, Addison's disease, rheumatoid arthritis, multiple sclerosis, celiac disease, and Sjögren's syndrome.

Results: The mean age of women was 41.94±0.5. The association rate of endometriosis with at least one autoimmune disease was 11.69%. There were 18 patients with autoimmune thyroiditis (7.8%), 9 patients with rheumatoid arthritis (3.9%), 4 patients with ulcerative colitis (1.7%), 2 patients with systemic lupus erythematosus (0.9%), 2 patients with Crohn's disease (0.9%), 1 patient with Addison's disease (0.4%), 1 patient with celiac disease (0.4%), 1 patient with multiple sclerosis (0.4%) and no patients with Sjögren's syndrome. No statistically significant differences were found between the stages of endometriosis in patients with or without autoimmune diseases.

Conclusion: To our knowledge, this is the only Türkiye-based study investigating the prevalence of autoimmune diseases in endometriosis patients. We examined the relationship between endometriosis and autoimmune disease depending on the endometriosis stage and patient age, but we could not reach a statistically significant conclusion. However, our data must be analyzed with caution due to the retrospective single-center study design and the small sample size.

Keywords: Endometriosis, autoimmune diseases, epidemiology

INTRODUCTION

Endometriosis is a chronic inflammatory disease that is distinguished by the existence of endometrial tissue outside the uterine cavity, most commonly on the pelvic peritoneum, ovaries, and fallopian tubes (1). The cardinal symptoms include severe pelvic pain, dysmenorrhea, dyspareunia, adnexal mass, and infertility (2, 3). According to studies conducted in the United States of America, the prevalence of endometriosis in women of reproductive age was found to be 5-10% (3). However, since surgical methods make the definitive diagnosis, the true incidence may not be determined clearly (3). The pathogenesis of endometriosis has not been fully elucidated yet, but it is known to be an estrogen-dependent chronic disease (1). Many theories have been put forward about the etiology of endometriosis, such as Sampson's theory of retrograde menstruation, coelomic metaplasia, and lymphovascular invasion theory (2). Among them, Sampson's retrograde menstruation theory is the most accepted, and it explains the formation of endometriosis due to the backward flow of blood in the normal menstrual cycle (4). However, a study demonstrated that although

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up to 90% of women experience retrograde menstruation, only 6-10% of them develop endometriosis (5). Although retrograde menstruation is seen in the majority of women, it has been assumed that endometriosis develops in women with congenital dysregulated immune mechanisms whose immune systems cannot respond to refluxed endometrial debris (6). This deficiency recalls the idea that the immune system cannot sufficiently remove the ectopic endometrium tissue. As demonstrated in earlier studies, menstrual debris is naturally removed by innate and adaptive immune system components followed by tissue restoration (1, 3, 6, 7). However, menstrual debris may cause "immune system overload" and "immune malfunction" over time. It is unclear whether this immunological deficiency is the consequence or the cause of endometriosis (6). Both cellular immunity and antibody-dependent immunity are impaired in endometriosis (8). Disruption of cellular immunity helps the implantation process of endometriotic cells in the peritoneum (7, 9). At the same time, the inability of peritoneal immune cells to eliminate the misplaced endometrium also leads to the ectopic development of endometrial tissue (7, 9). In addition, it is observed that the cytotoxic activity of natural killer cells is decreased in patients with endometriosis (10). Consequently, the endometrial cells in the peritoneal cavity can remain present for an extended period, increasing the probability of their adherence (10). In a study comparing the serum of 71 laparoscopically staged endometriosis patients and 109 healthy individuals, antibodies to nuclear, phospholipid, smooth muscle, and sperm antigens were investigated, and at least one type of the abovementioned antibodies was found in 58% of endometriosis patients (11). In addition, antinuclear antibodies, smooth muscle antibodies, anticardiolipin antibodies, and lupus anticoagulant levels were found to be significantly higher in endometriosis patients compared to the control group (11). Based on this connection between endometriosis and the immune system, we believe autoimmune factors might be more prominent than currently thought in the pathophysiology of the disease. Therefore, autoimmune diseases are seen more often in women with endometriosis. In this retrospective study, 231 women with endometriosis were admitted to the Department of Gynecology and Obstetrics, Trakya University Hospital, were included and examined in terms of other autoimmune diseases, and we aimed to determine the prevalence of autoimmune diseases in women with endometriosis.

MATERIAL AND METHODS

This study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (protocol code: TÜTF-BAEK 2021/235, date: 17.05.2021). Data for this retrospective epidemiological study was collected through the database of Trakya University School of Medicine between January 2014 to 31 December 2021. Two hundred thirty one women older than 18 years old that were identified with endometriosis were included in the study. The inclusion criterion was a diagnosis of endometriosis confirmed by surgery and pathology. The staging was performed by the location, size, and type of lesions and the extent of adhesions present by using the revised scoring system of the American Society for Reproductive Medicine (rASRM) (12). Scoring system of the American Society for Reproductive Medicine Stages for endometriosis is first defined in 1979 and revised in 1997. rASRM is the most widely used staging method for endometriosis. With this way, score is determined by the location, infiltration and posterior culdesac obliterations of the endometriotic lesions. It has 4 different stages: I (1-5 points, minimal), II (6-15 points, mild), III (16-40 points, severe), and IV (>40 points, extensive). Data for staging, patient age, and the presence of any comorbid autoimmune disease, regardless of the time of diagnosis, were recorded. Included diagnoses of autoimmune diseases did fulfill the diagnosis requirements of International Classification of Diseases-10 (13). Considered autoimmune diseases were systemic lupus erythematosus (SLE) (M32.1), inflammatory bowel disease (Crohn's disease and ulcerative colitis) (K50 and K51), autoimmune thyroiditis, Addison's disease (E27.1), rheumatoid arthritis (RA) (M06.9), multiple sclerosis (MS) (G35), celiac disease (K90.0), and Sjögren's syndrome (M35.00) (13). Patients with negative clinical signs or autoimmunity markers were considered as patients without autoimmune diseases.

Statistical Analysis

The data were analyzed with IBM SPSS version 23.0. Nominal variables were expressed as total count and percentage. Age was expressed as mean (± standard deviation). Normality of the data was determined via Shapiro-Wilk test and statistical comparison of groups was performed by chi-square test or Fisher's exact test as appropriate. Statistical comparison of parametric variables among the groups was performed by Independent sample t-test. For all analyses, a p-value threshold of <0.05 was set for statistical significance.

RESULTS

Among 231 patients in this study, 204 did not have an autoimmune disease, 27 had one or more autoimmune diseases, and the distribution of these 27 patients was as follows: 20 patients had only one autoimmune disease, 4 had two autoimmune diseases, 2 had three autoimmune diseases and 1 had four autoimmune diseases. The association rate with at least one autoimmune disease was 11.69%. The number of diagnoses of co-existing autoimmune diseases is as follows, regardless of whether patients have one or more diagnoses: 18 patients with autoimmune thyroiditis (7.79%), 9 patients with RA (3.90%), 4 patients with ulcerative colitis (1.73%), 2 patients with SLE (0.87%), 2 patients with Crohn's disease (0.87%), 1 patient with Addison's disease (0.43%), 1 patient with celiac disease (0.43%), 1 patient with MS (0.43%) and no patients with Sjögren's syndrome. The mean age of patients with endometriosis was 41.94±0.5. No statistically significant difference was found in the mean age of patients with autoimmune diseases (40.6±7.4 years) and without autoimmune diseases (42.1±8.9 years) (p=0.364) (Figure 1).

There were 20 patients with stage I (8.7%), 2 patients with stage II (0.9%), 171 patients with stage III (74%), and 38 patients with stage IV (16.5%) endometriosis. Among patients who did not have autoimmune diseases 17 (8.3%), 2 (1%), 151 (74%), and 34 (16.7%) patients had stage I, II, III, and IV endometriosis, respectively. Whereas among patients with autoimmune diseases 3 (11.1%), 20 (74.1%), and 4 (14.8%) patients had stage I, III, and IV endometriosis, respectively. Patients who had autoimmune diseases with stage II endometriosis were not found. No statistically significant difference was found between the stages of endometriosis in patients with or without autoimmune diseases (p=0.913) (Figure 2).

DISCUSSION

Current studies strengthen the theory that endometriosis may be an autoimmune disease (7-10). The fact that endometriosis does not occur in every woman with retrograde menstruation suggests that while this debris can be easily cleaned in women with a healthy immune system, the disease occurs due to the debris that cannot be cleaned well in individuals with immune defects (6). However, it is still unclear whether immune disorders can cause endometriosis or whether these diseases occur secondary to events resulting in endometriosis (7). In our study, 231 patients were examined, and the association rate with at least one autoimmune disease was 11.69%. The study by Caserta et al. (14) showed that patients with endometriosis have a higher rate of coexistence of autoimmune diseases than those without. Another study examined 3680 female patients surgically diagnosed with endometriosis and found that patients with endometriosis had higher rates of hypothyroidism, RA, SLE, Sjögren's syndrome, and MS, but not hyperthyroidism or autoimmune diabetes, compared to the general population (15). Further, a study in Denmark with data from 37661 patients showed an association between endometriosis and MS, SLE, and Sjögren's syndrome (16). We found that autoimmune thyroiditis was the most frequently associated with endometriosis among autoimmune diseases, with a rate of 7.79%. A cross-sectional study by Petta et al. (17) detected 38 autoimmune thyroiditis patients among 148 endometriosis patients and calculated this rate as 25.67%. In the study of Ek et al. (18), elevated Immunoglobulin G titers of thyroid stimulating hormone receptor antibody were found to be associated with endometriosis, which supports the link between endometriosis, autoimmunity, and thyroid pathophysiology. However, a more recent study showed an increased risk of Graves' disease but did not find an increased risk of hypothyroidism or autoimmune hypothyroid disease (19). The coexistence of RA and endometriosis was found to be 3.9%. In addition, patients with endometriosis were associated with an increased risk of RA in the retrospective cohort study of Xue et al. (20). However, Ek et al. (18) examined the relationship between endometriosis and RA, and no association was found. In a case-control study of 223 patients, in which the coexistence of celiac disease and endometriosis was investigated, 7 patients (3.1%) had celiac disease (21). In our study, which included 231 patients, this rate was 0.4%. Although the sample sizes are close, the coexistence of endometriosis and celiac disease detected in our study was 1 in 8 compared to the result obtained by the other study (21). In our study, the coexistence of Crohn's disease or ulcerative colitis with endometriosis was 0.87% and 1.73%, respectively. The study by Jess et al. (22) reported an increased incidence of inflammatory bowel diseases (Crohn's disease and ulcerative colitis) in women with a history of endometriosis compared to women without known endometriosis. Our study found the association between SLE and endometriosis to be 0.87%. In a cohort study, 37661 women diagnosed with endometriosis were examined, and a statistically significant 1.6-fold increase in the risk of SLE was observed (16). Another nationwide population-based cohort study revealed that patients with endometriosis are at increased risk of SLE and that adequate hormonal therapy can reduce the risk of SLE (23).

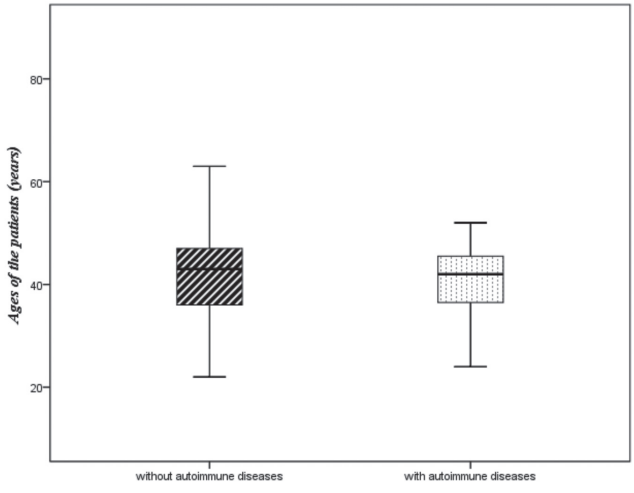

Figure 1: Boxplots of the distribution of patients' ages in endometriosis without and with autoimmune diseases.

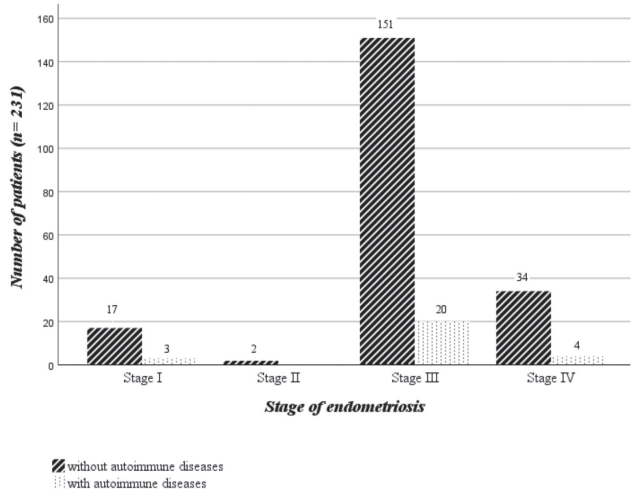

Figure 2: Comparison of the number of patients with and without autoimmune diseases in different stages of endometriosis.

We found that 1 patient had Addison's disease (0.43%) in our study. Gemmill et al. (24) reported that the prevalence of Addison's disease in women with endometriosis was higher compared to all women (2.31 per 1000 population versus 0.09 per 1000 population). While the association of MS was detected in 0.43% of our study, we could not find concomitant Sjögren's disease in 231 endometriosis patients. In a cross-sectional study conducted by Sinaii et al. (15), it was found that the incidence of Sjögren's syndrome was higher in women with endometriosis. MS was the least associated disease, with a rate of 0.43%. In a study with 16 patients with relapsing-remitting MS, assisted reproductive technology using gonadotropin-releasing hormone agonists and recombinant follicle-stimulating hormone for the treatment of infertility was found to be associated with a 7-fold increase in the risk of MS exacerbation (25). This has shown that hormonal factors also play an essential role in increasing the activity or severity of autoimmune diseases. We also examined the relationship between endometriosis and autoimmune disease depending on the endometriosis stage and patient age, but we could not reach a statistically significant conclusion. In light of all this information, there are many studies trying to explain the relationship between autoimmune diseases and endometriosis, but they were either conducted in a single center or focused on a single disease. If there is a pathophysiological correlation, the only way to elucidate it is to conduct more comprehensive studies. We looked up a possible relationship between endometriosis and several autoimmune diseases, that could be reached on our hospital database. As a result, we did not find any remarkable associations with a high percentage. The strength of our study is the first and only Türkiye-based study investigating the prevalence of autoimmune diseases in endometriosis patients. However, since our sample size was small (n=231), slight differences in the number of patient groups were reflected as relatively remarkable differences in percentages. Since the definitive diagnosis of endometriosis in the current literature can only be made with the pathological examination of a surgical sample, many patients can be overlooked. In addition, retrospective analysis of the hospital database brought some limitations to the study. There were missing data because some patient data were incompletely processed into the database. In addition, since the data were analyzed retrospectively, the patient's data (e.g., biochemical results, CA-125 values) that were not examined at the time of diagnosis could not be examined later, and these data could not be compared. The pathophysiology of endometriosis can be clarified by further studies investigating the association between various autoimmune diseases and endometriosis, and thus treatment methods for endometriosis can be improved. Furthermore, multicenter studies with a large sample size are required to deepen our understanding of endometriosis in Turkey.

CONCLUSION

In this retrospective single-center study with a small sample size, the prevalence of at least one autoimmune disease in patients with endometriosis is 11.69%. Clinicians should keep in mind that patients with endometriosis may also have additional autoimmune diseases and possible endometriosis in autoimmune patients. Further research may help understand the association between endometriosis and the immune system.

Ethics Committee Approval: *This study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (protocol code: TÜTF-BAEK 2021/235, date: 17.05.2021).*

Informed Consent: *Retrospective study.*

Conflict of Interest: *The authors declared no conflict of interest.*

Author Contributions: *Surgical and Medical Practices: S.B., S.S., E.B.K., M.S.Y., E.K., O.B., S.A., K.E., Concept: S.B., S.S., E.B.K., M.S.Y., E.K., O.B., S.A., K.E., Design: S.B., S.S., E.B.K., M.S.Y., E.K., O.B., S.A., K.E., Data collection or processing: S.B., S.S., E.B.K., M.S.Y., E.K., O.B., S.A., K.E., Analysis or Interpretation: S.B., S.S., E.B.K., M.S.Y., E.K., O.B., S.A., K.E., Literature Search: S.B., S.S., E.B.K., M.S.Y., E.K., O.B., S.A., K.E., Writing: S.B., S.S., E.B.K., M.S.Y., E.K., O.B., S.A., K.E.*

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CASE REPORT

SPINAL ARACHNOID CYST: A CASE REPORT

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ABSTRACT

Arachnoid cysts are categorised into cranial and spinal types and are usually asymptomatic. Spinal arachnoid cysts are rare. In large dimensions, the cyst may require surgery. In this case report, we aim to evaluate a patient with spinal arachnoid cyst and the surgery to remove the cyst. A 70-year-old patient applied to the clinic with the complaint of losing balance while walking. No additional symptoms were found in the examination. Magnetic resonance imaging showed a cystic lesion of 25x21x11 mm size located in the anterior area at the T2 level, suggesting an arachnoid cyst. The patient was operated on, and the cyst was removed. The patient was discharged without complaints. There were no problems during the follow-up period. Spinal arachnoid cysts are uncommon; however, when present, they might cause pathological findings in patients. They are usually found incidentally on radiological imaging performed for another reason. The treatment decision should be made considering the complaints of patient, localisation of cyst, and size of cyst.

Keywords: Arachnoid cysts, excision, spinal cysts

INTRODUCTION

Arachnoid cysts (AC) are cerebrospinal fluid accumulations in the arachnoid membrane. Even though they are mostly intracranial, they can also be observed in the spinal cord (1). In the spinal cord, spinal AC (SAC) are usually seen in the thoracic region (2). The size and location are the main factors in symptom presentation (3). The most common symptoms are headache, dizziness, nausea, vomiting, ataxia, seizures, and hearing loss. In infancy, hydrocephalus is also a common symptom. On the other hand, SAC give symptoms of the pressure they make on the spinal cord. The patient may present to the clinic with lower back pain, numbness, or weakness in the legs. The formation mechanisms are unclear; most of them are thought to be congenital. Congenital ones are called primary AC. Other predicted formation mechanisms are traumas and infections, especially in the first two decades, named secondary AC (4). To our knowledge, the genetic factor should always be considered. Previous literature shows that mutation in the *FOXC2* gene may cause AC (5). It may also have an association with genetic diseases such as Marfan syndrome (6). SAC are rare. Approximately 2% of the spinal cysts are identified as AC. Those are not usually the reason for the patient's presentation to the clinic; they are diagnosed incidentally. Generally, AC are asymptomatic, but various symptoms may be present depending on their location and size (1). AC are seen in a higher prevalence in men; however, it is not possible to give an exact ratio of the frequency in the population due to the probability of many undiagnosed cysts (7). Although magnetic resonance imaging (MRI) is the gold standard for diagnosis, computed tomography (CT) is also sufficient at diagnosis of arachnoid cyst (8, 9). If the patient has no symptoms, AC can be followed up with imaging every six months or a year. Conservative treatment is preferred in most patients. Invasive methods such as endoscopic procedures, open craniotomy fenestration, shunting, and marsupialization are preferred in patients with severe symptoms (1). The aim of this case report is to report an arachnoid cyst that is detected in an

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elderly male patient, which was previously operated with the diagnosis of meningioma.

CASE REPORT

A 70-year-old male patient was admitted to the department of neurosurgery of Trakya University School of Medicine with a complaint of dizziness during walking. Cerebellar condition was tested. Romberg and Fukuda tests were positive, patience balance was disordered. The patient did not have any other complaints. The patient's physical examination was unremarkable. He had no motor weaknesses, sensory loss, or pathological reflexes. Cervical and cranial MRIs were requested since it was known that the patient was previously operated on for meningioma five years ago. In addition to the anticipated postoperative changes in the cranial frontoparietal region, a cystic lesion with hypodense nodularity that may belong to the debris-solid component was observed. It was measured 25 mm in the long axis in the coronal plane and 21x11 mm in the axial plane, located in the anterior epidural area at the T2 vertebra level (Figure 1). An arachnoid cyst was considered a preliminary diagnosis. An operation decision was made, and routine preoperative examinations were completed. The operation was started with a midline incision between T1-T3 spinous processes. Paravertebral muscles and fascia were detached unilaterally, and T2 left hemilaminectomy was performed. After local excision of the ligamentum flavum, and dural opening, a cystic mass was located under it (Figure 2) and removed in two parts (Figure 3). It was observed that compression decreased dramatically after excision. After the meticulous water-tight closing of the dura, a drain was placed in the epidural space, and the surgery was completed. The patient was awakened uneventfully and hospitalized in the neurosurgery department. The postoperative examination was regular; no neurological deficit was detected. A postoperative MRI showed the total removal of the cyst. The patient's condition was stable on the fourth postoperative day, so he was discharged. The follow-up period of three months was uneventful, and the patient's complaints regressed dramatically.

Pathology

The cyst was excised in two pieces and sent to the pathology department for macroscopic and microscopic examination. An off-white lesion measuring 2.5x0.5 cm was formed as the pieces were combined. Histopathologically, the epithelium of AC was lined with a single layer of mature arachnoid (Figure 4). Rarely, meningothelial hyperplasia could be seen in focal foci (Figure 5). A fibrous membrane and sparse structure could be observed. The immunohistochemical study showed a reaction in the arachnoid event with epithelial membrane antigen (Figure 6).

DISCUSSION

Spinal arachnoid cysts are rare benign structures; the formation mechanism has not yet been determined. It is known that SACs are usually located extradural, as reported by Yaltırık et al. (10). Although the exact mechanism of formation is not known,

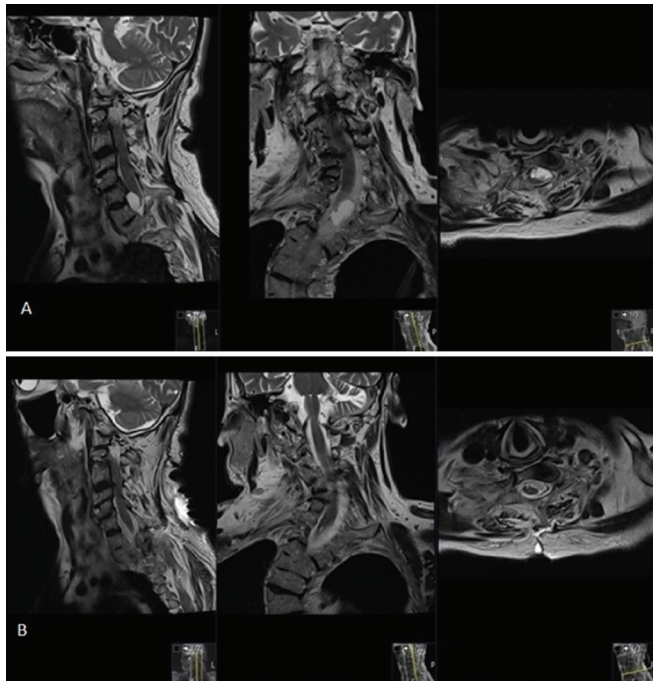

Figure 1: A: Preoperative magnetic resonance imaging in the sagittal, coronal, and axial plane, **B:** Postoperative magnetic resonance imaging in the sagittal, coronal, and axial plane.

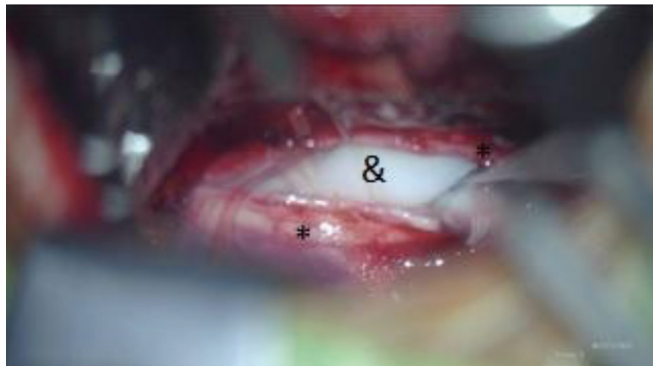

Figure 2: After dural incision a cystic mass was located. The dura mater (asterisk). The cyst (&).

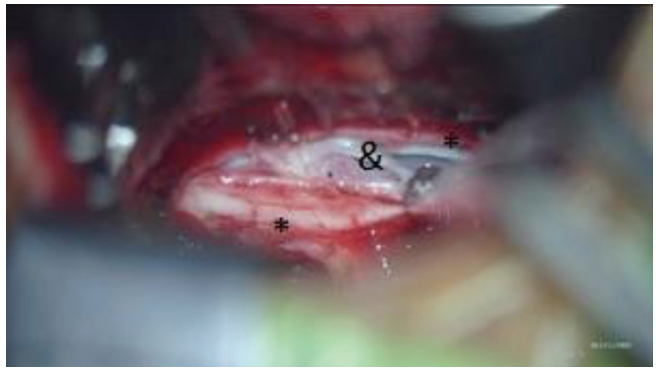

Figure 3: The cystic mass was excited in two parts. The dura mater (asterisks). The cyst (&).

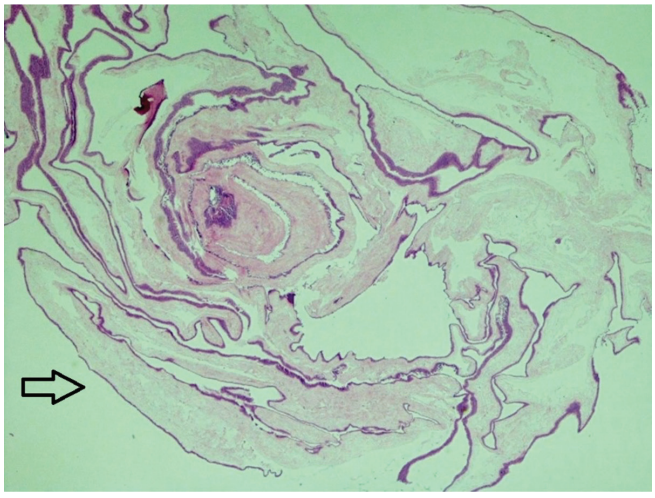

Figure 4: Cystic formation with an epithelial and fibrous membrane consisting of a single row of arachnoid cells (arrow) (hematoxylin and eosin, x40 magnification).

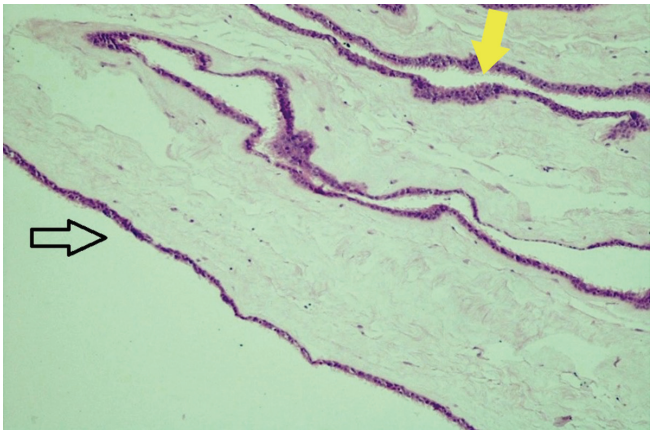

Figure 5: The cyst epithelium was lined with a single row of arachnoid cells (black arrow). Meningothelial hyperplasia may be seen in focal areas (yellow arrow) (hematoxylin and eosin, x200 magnification).

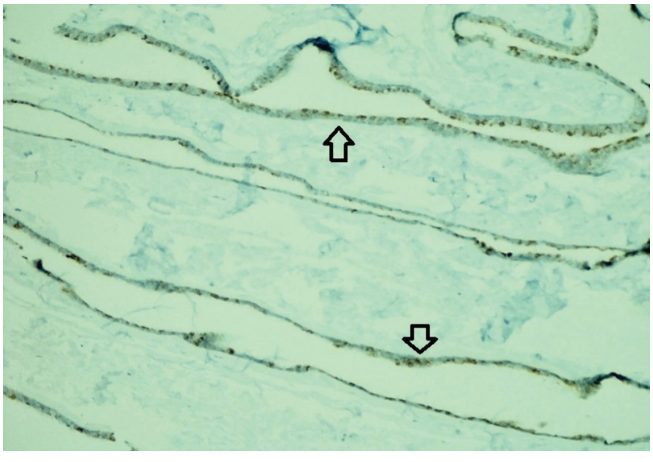

Figure 6: Arachnoid cells showing epithelial membrane antigen immunoreactivity (arrows) (epithelial membrane antigen immunohistochemistry, x200 magnification).

previous trauma and infection are considered important risk factors. Our patient reported neither of them. However, he had a history of a recent cranial operation. The absence of any lesion in the patient's previous imaging suggests that the cyst formed after the operation. This condition is rare because ACs are usually congenital and diagnosed in the first two decades. There are publications in the literature about ACs related to several diseases. Dandy-Walker syndrome is reported to be one of them (11). One study reported that some SAC patients had headaches that started with exercise (6). Therefore, it would be reasonable to request an MRI in patients presenting with a similar anamnesis, keeping the diagnosis of AC in mind. In almost all studies on AC, MRI and CT have been used together for accurate diagnosis and treatment (8). CT may be the first step to have a suspicion of an AC; however, final diagnosis must be proved by MRI (8). In our case, we also decided to investigate with dual imaging. Patients with SACs may be followed up by MRI and CT if patients do not have neurological symptoms or increased intracranial pressure. The aim of treatment in AC is to provide a connection between the content of the cyst and the anatomical corridors of cerebrospinal fluid flow or to place a shunt system between the cyst and other body cavities where resorption can be achieved. The location of the cyst is important in determining the surgical treatment method of AC. The indication for endoscopy should also be reviewed for each patient. The age of the patient, anatomical features of the cyst, the relationship of the cyst with the surrounding cisterna and vascular structures are the factors affecting the use of the endoscope. In line with the detailed information provided by the constructive interference in steady state sequence, it is possible to make realistic plans regarding especially endoscopic surgical techniques, possible cysto-cisternostomy and cysto-ventriculostomy options (12). SAC are rare benign formations that might require treatment when they lead to neurological symptoms. Complete excision and, if possible, dural repair should be performed when surgery is required, but follow-up is usually sufficient. The decision should be made by considering the patient's clinical, radiological, and demographic characteristics, and by including the patient and their relatives in the decision process.

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CASE REPORT

FORGOTTEN DOUBLE-J STENT WITH BLADDER STONE FORMATION: A PEDIATRIC CASE

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ABSTRACT

Although double-J catheters are the most commonly used tools in urology practice, it can cause many complications. One reason for such complications is excessive indwelling time. The aim of this case report is to examine the complications caused by a catheter forgotten in the patient's body and to prevent similar complications from occurring with the knowledge gained. A 7-year-old female patient was admitted to our hospital with difficulty urinating that has been going on for 10 days. She had a history of kidney stones, and a double-J catheter was placed in her kidneys at a different health institution 1 year ago. It was found later on that a bladder stone about 2 cm in size was formed around the double-J catheter. Transition to an open surgery was made. The catheter had completely passed through the stone, and when the stone was removed, the catheter came out with it.

Keywords: Bladder stone, catheter, urology

INTRODUCTION

Double-J catheters are tools placed in the ureter to provide urine drainage from the upper urinary tract and are commonly used in urology practice. Ureteral stents were first reported in 1967 by Zimskind et al. (1) and the term "double-J stent" was introduced later in 1978 by Finney (2). Since then, many modifications to its design were made to allow easier manipulation and to reduce the risk of encrustation and infection (3). They are favored tools in the treatment obstructive anuria, renal reconstructive surgical operations, and renal transplantations (4). Over 80% of urologists state that they place double-J catheters post-operation (post-op) in more than half of all their cases (4). However, their usage may lead to serious complications such as migration, fragmentation, hematuria, bladder irritation, blockage, infection, and encrustation with long-term stent duration. El-Faqih et al. (5) state that encrustation risk is increased with stent indwelling time, which was evident in more than 76% of patients after the 12th week of placement. Usually, the removal of double-J catheters is a rather simple endourologic maneuver, however, there is an increased risk of breakage and fragmentation with a longer dwelling time. Therefore, it can be formidable to navigate and plan the proper treatment. Combinations of endourological and open surgery have been used for removal of forgotten double-J stents, but there are only a few case reported in literature (6). In this case report, we present a forgotten double-J catheter causing a bladder stone in a female patient whose full treatment was refused after the operation. We aim to showcase the importance of providing the necessary knowledge necessary to prevent such cases from occurring.

CASE REPORT

A 7-year-old female patient was admitted to Pediatric Surgery Department of Trakya University School of Medicine Hospital with a complaint of urinating difficulty which lasted for 10 days. She had a history of kidney stones, and a double-j catheter was placed in her right kidney as a treatment for kidney stones at a different health institution a year prior. The results of the physical examination, renal functions tests and other laboratory examinations were normal. The graphs and the urinary

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ultrasonography showed an opacity with a 2 cm radius in their bladder. The patient was admitted to the pediatric surgery ward with planned cystoscopic laser lithotripsy. After the pre-operative examinations and follow-up results came out normal, the patient was taken to operation. The patient was put in lithotomy position. When the pediatric cystoscope was passed through the urethra into the bladder, a bladder stone with a radius of approximately. 2 cm on the end of a double-J catheter from the right kidney was spotted. It was decided that it was no suitable for lithotripsy because of the size of the stone. Therefore, transition to open surgery was decided. The bladder was opened with a vertical incision by placing 2 hanging sutures in the bladder. The catheter was passed through the stone, and when the stone was removed, the catheter came out with the stone. After these procedures, the patient was closed up. A 10 fr sole probe was placed in the patient's bladder, concluding the procedure.

No early complications were observed after surgery. The patient left the operating room without any problems. The patient started receiving ampicillin-sulbactam. Foley catheter was followed up with the probe. On the first day of post-op the patient began oral feeding. On the fifth day of post-op, the foley catheter was taken away, after which a spontaneous urine output began. On the sixth day of post-op; after the usual follow-up and examinations, an oral antibiotic prescription was given, and the patient was taken to the outpatient clinic and discharged (Figure 1).

DISCUSSION

Double-J catheters have been used in urology practice for a long time to ensure smooth urine drainage (7). Although it is a practical and reliable tool, it has been found that it can bring various complications with it. One reason for such complications is exceeded indwelling time in the body due to reasons such as forgetfulness. Many studies have consistently assessed the retention of stents in the body for more than 3 to 6 months (8). Our patient presented to us with a stent that was inserted approximately one year prior. Stationary urine in the bladder is prone to stone formation. The catheter encounters this stationary urine in the bladder and forms a focus as a foreign body easily adhering to crystals that cause stones, causing accumulation and large stones (9).

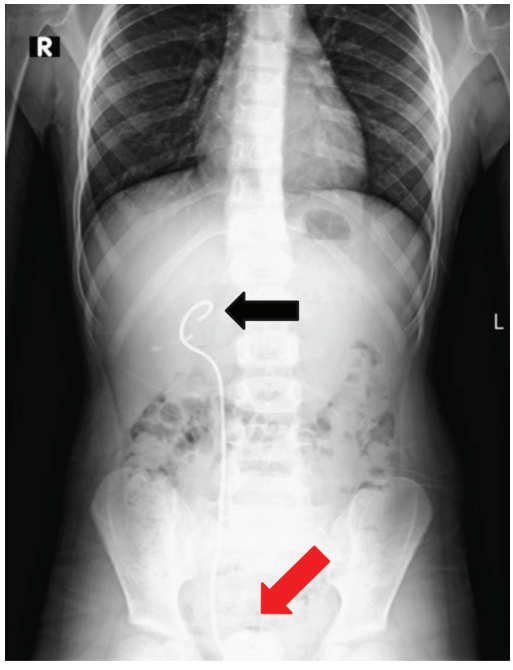

Figure 1: The radiograph of the patient's urinary tract. A double-J catheter placed in the right kidney (black arrow) and a kidney stone (red arrow).

The length of time that the stent can stay in the body after it is inserted may vary depending on the stent's type. When we compare the durability and usage times of stents in terms of the types of materials used according to the studies done, we see that silicone-containing stents have a shorter duration as well as fewer side effects (10). In addition to silicone stents, stents containing polyurethane, silica, percuflex and hydrogel-coated polyurethane are also used in urology practice (10). The most common complications seen in other reported cases related to forgotten stents are patient incompatibility, abdominal and side pain, hematuria, migration, bacteriuria, irritable bladder symptoms, and loss of kidney function (10). In our case the patient was presented to us with complaints of hematuria and suprapubic pain. Further examinations showed that the forgotten stent was encrusted throughout its length. Endourological methods for removing forgotten stents on the body, open surgical methods, lithotripsy, and medical therapy can be used together or separately (7). According to Monga et al. (11) in 31 patients, they examined the remaining double-J stents for a longer period and performed ureteroscopy, percutaneous nephroscopy, cystolithotripsy, extracorporeal shockwave lithotripsy, cystolithotonomy, and nephrectomy in their patients (10). There are several cases of severe stent encrustation in the literature. Most of the cases described have a stent indwelling time of more than 6 months and they rarely require open surgery. Aboutaleb (12) describes a patient with a forgotten stent of 10 years that was fully encrusted with multiple ureteral stones and bladder calculus. They underwent cystolithotripsy, ureteroscopic laser lithotripsy, and stent removal. In another case that is presented by Al-Hajjaj et al. (13) open surgery was performed to remove two bladder stones and the forgotten stent. Another severe bladder encrustation case that was caused by a forgotten double-J catheter was treated with cystolithotripsy (14). In our case, the double-J catheter was removed from the patient and a foley probe was inserted with an operation. Although hospitalization and follow-up were advised to the children's service, the patient's family signed the rejection form and ensured the patient's exit from the hospital.

To avoid forgetting the catheter and the complications that may develop after it, the patient should be provided with appropriate information after the catheter is inserted. The procedure applied to the patient, the necessary care, and follow-up of the procedure should be explained clearly to the patient. Recent

studies also show that a mobile monitoring system could be an efficient way to track inserted catheters to prevent time related complications (15).

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