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Thrombophilia and Screening in Family Medicine Practice

ABSTRACT
Thrombophilia encompasses a group of inherited or acquired disorders that predispose individuals to thrombotic events. The identification of these individuals is essential to guide appropriate management strategies and reduce the risk of complications and the associated increased healthcare costs and mortality. Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), represents a major global health concern due to its substantial morbidity and mortality rates. General practitioners (GPs) play a vital role in the assessment and initial screening of patients for thrombophilia, as they perform their activities at the entrance of the health care system - in primary care. In addition, they serve a heterogeneous group of patients - from newborns to pregnant women and adults, knowing their risk factors and underlying diseases well. In general practice, an enduring doctor-patient relationship is usually established and the medical history is documented and well known, making it possible to carry out screening initiated in general practice with great success. The most common genetic defects that lead to thrombophilia are Factor V Leiden mutation, Prothrombin gene mutation, Protein C deficiency, Protein S deficiency, Antithrombin deficiency. Multiple acquired conditions have also been linked with an increased predisposition towards VTE development, including oral contraceptive use, hormone replacement therapy (HRT), pregnancy, postpartum period and malignancy. Thrombophilia screening in general practice should be guided by clear indications to identify individuals at increased risk of thrombotic events.
Keywords: Thrombophilia, Hereditary, Acquired, Thrombosis, Screening, General Practitioners.

Aile Hekimliği Pratiğinde Trombofili ve Tarama

ÖZET
Trombofili, bireyleri trombotik olaylara yatkın hale getiren bir grup kalıtsal veya edinilmiş bozukluğu kapsar. Bu bireylerin tanımlanması, uygun yönetim stratejilerine rehberlik etmek ve komplikasyon riskini ve buna bağlı olarak artan sağlık hizmeti maliyetleri ve mortaliteyi azaltmak için önemlidir. Derin ven trombozu (DVT) ve pulmoner emboliyi (PE) kapsayan venöz tromboembolizm (VTE), önemli morbidite ve mortalite oranları nedeniyle önemli bir küresel sağlık sorununu temsil etmektedir. Pratisyen hekimler (GP'ler), faaliyetlerini sağlık sisteminin girişinde - birinci basamakta - yerine getirdiklerinden, hastaların trombofili açısından değerlendirilmesinde ve ilk taranmasında hayati bir rol oynamaktadır. Ayrıca yenidoğanlardan hamilelere ve yetişkinlere kadar heterojen bir hasta grubuna, risk faktörlerini ve altta yatan hastalıkları iyi bilerek hizmet veriyorlar. Pratisyen hekimlikte genellikle kalıcı bir doktor-hasta ilişkisi kurulur ve tıbbi geçmiş belgelenir ve iyi bilinir; bu da pratisyen hekimlikte başlatılan taramanın büyük bir başarıyla gerçekleştirilmesini mümkün kılar. Trombofiliye yol açan en yaygın genetik bozukluklar Faktör V Leiden mutasyonu, Protrombin gen mutasyonu, Protein C eksikliği, Protein S eksikliği, Antitrombin eksikliğidir. Oral kontraseptif kullanımı, hormon replasman tedavisi (HRT), hamilelik, doğum sonrası dönem ve malignite dahil olmak üzere birden fazla kazanılmış durum, VTE gelişimine yatkınlığın artmasıyla da ilişkilendirilmiştir. Genel pratikte trombofili taraması, trombotik olay riski yüksek olan bireyleri belirlemek için açık endikasyonlara göre yönlendirilmelidir.
Anahtar Kelimeler: Trombofili, Kalıtsal, Edinsel, Tromboz, Tarama, Pratisyen Hekimler.

INTRODUCTION

Thrombophilia encompasses a group of inherited or acquired disorders that predispose individuals to thrombotic events. The identification of these individuals is essential to guide appropriate management strategies and reduce the risk of complications and the associated increased healthcare costs and mortality. Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), represents a major global health concern due to its substantial morbidity and mortality rates. Approximately 10% of cases are fatal within one month after diagnosis, emphasizing the importance of timely detection measures targeting high-risk individuals (1). General practitioners (GPs) play a vital role in the assessment and initial screening of patients for thrombophilia, as they perform their activities at the entrance of the health care system - in primary care. In addition, they serve a heterogeneous group of patients - from newborns to pregnant women and adults, knowing their risk factors and underlying diseases well. In general practice, an enduring doctor-patient relationship is usually established and the medical history is well knonn and documented, making it possible to carry out screening initiated in general medical practice with great success. This review aims to consolidate the current knowledge and evidence on thrombophilia screening in general practice, highlighting the key indications, testing strategies, and implications for patient management.

METHODS

A comprehensive literature search was conducted using electronic databases, including PubMed, Medline, and Cochrane Library, to identify relevant articles published between 2010 and 2021. The search terms included "thrombophilia," "screening," "general practice," and combinations thereof. Only studies published in English and those focusing on thrombophilia screening in general practice were included. Reference lists of selected articles were also reviewed to identify additional relevant studies.

Types of Thrombophilia: Thrombophilia includes heterogeneous types of etiological causes of coagulation disorders, which are divided into two large groups - hereditary and acquired, but often there is a combination of these factors (2).

Hereditary thrombophilia: Hereditary thrombophilia is due to genetic defects, which can be in the homozygous state or a combination of two or more heterozygous factors, and then the clinical manifestation is at an early age. The existence of single heterozygous states is usually established by laboratory testing (3). The coagulation system in humans includes hemostatic and fibrinolytic pathways, and a defect at any one level leads to a disturbed balance and the appearance of a pathological condition. The two systems are enzyme and are interconnected, regulating formation and breakdown of fibrin. The end result of the coagulation cascade is to produce thrombin, which can then convert soluble fibrinogen into fibrin, which forms a clot. Coagulation is initiated when factor VIIa binds to tissue-factor (TF) on the surface of endothelial cells and monocytes at sites of vascular injury. The TF-factor VII complex activates factor IX and X to factors IXa and Xa, respectively. Factor Va and Xa, together, activate prothrombin to thrombin. Thrombin has multiple prothombotic roles: it cleaves soluble fibrinogen to insoluble fibrin that will eventually form the hemostatic plug, and activates factors V, VIII, XI and XIII. Thrombin also acts to produce an anticoagulant effect by forming an enzyme complex with thrombomodulin to activate protein C (4). Activated coagulation factors are modulated by natural inhibitors circulating in the plasma, the most important of which are antithrombin, protein C, and protein S (5). According to data, 15% of patients with pulmonary embolism before 45 years of age have a hereditary deficiency of one of the mentioned factors (5). The imbalance between reduced inhibitors of coagulation and/or increased activation of coagulation factors leads to thrombosis (5). Plasmin plays a central role in the fibrinolytic system, with the ultimate goal being the destruction of thrombi formed in the vascular system. Their basic structure involves thrombin, which is degraded by plasmin. Tissue-type plasminogen activator (t-PA) and urokinase (u-PA) activate plasminogen, which is the inactive form of plasmin. Thrombophilia can also occur with plasminogen deficiency (6). The most common genetic defects that lead to thrombophilia are Factor V Leiden mutation, Prothrombin gene mutation, Protein C deficiency, Protein S deficiency, Antithrombin deficiency. Dysfibrinogenemias and Hyperhomocysteinemia are rare. Most probably there are still undiscovered types, which is why the frequency of hereditary thrombophilia cannot be precisely defined (4).

Characteristics of the most common genetic defects.

Pediatric Patients: In the pediatric population, genetic defects in coagulation lead to neonatal purpura fulminans, renal vein thrombosis, vena cava thrombosis and hepatic venous thrombosis, pulmonary embolism, Legg Calve Perthes and cerebral palsy (7). In homozygous individuals with protein C or S deficiency, the clinical picture is neonatal purpura fulminans and disseminated intravascular coagulation with an incidence of about 1 in 16,000–360,000 (8). Newborns with hereditary forms of thrombophilia have demonstrated a higher risk for thromboembolic complications compared to older children. It was established that their frequency decreases significantly after the first year of life, with a second peak during puberty and adolescence

and is associated with reduced fibrinolytic activity (4).

Factor V Leiden Mutation (V Q506 or Arg506Gln): In this type of defect, there is an allele that makes factor V resistant to the proteolytic effect of protein C. A transition (guanine to adenine) at nucleotide 1691 results in the replacement of arginine by glutamine. Thus, the cleavage at position 506 by activated protein C becomes impossible, and as a result, the availability of factor Va and thus the synthesis of thrombin increases, resulting in a hypercoagulable state. The main clinical manifestation is deep venous thrombosis with or without pulmonary embolism, as well as thrombosis of placental vessels with a probable association with recurrent pregnancy loss (9). In a study of 34 families with this mutation, it was found that by the age of 50, 25% of them will develop thrombotic complications. Homozygous carriers have an 80-fold higher risk of these events and will develop at least one by the end of their lives (10). These results are supported by another study of 306 individuals from 50 Swedish families, in which 40% of homozygotes had a thrombotic event by age 33 compared with 20% in heterozygotes and 8% in healthy controls. According to data from European studies, the frequency of heterozygotes is 5-8% and up to 15% in some areas of Greece, Sweden and Lebanon.

Prothrombin Gene Mutation (G20210A): In a study of 28 families from the Netherlands who survived venous thromboembolism, a substitution of guanine to adenine at nucleotide 20210 in the 3' untranslated region of the prothrombin gene was identified (11). Prothrombin (factor II) has procoagulant, anticoagulant and antifibrinolytic activities, which is why the mutation leads to the manifestation of multiple defects in coagulation. Patients with this type of mutation have an increased risk of venous thrombosis, but less than that of factor V Leiden (10). In them, 30% higher plasma levels of prothrombin were found compared to healthy people. According to data from 11 European centers, the frequency of this mutation is 0.7-4.0%

Protein C Deficiency: The gene for protein C is located on chromosome 2 (2q13–14) and the defect is inherited in an autosomal dominant manner. There are two major subtypes of heterozygous protein C deficiency, and more than 160 genetic abnormalities have been identified (12). In homozygotes, purpura fulminans has been observed in the neonatal period (13). An increased risk of warfarin-induced skin necrosis has been reported in heterozygotes (14). In pregnant women, this type of genetic defect is associated with the development of DVT, preeclampsia, intrauterine growth restriction and recurrent pregnancy loss (15). According to data from studies in the Netherlands, in most patients, the appearance of thrombotic complications increases towards the age of 50 and up to 20 years of age they are usually asymptomatic (16). A study of 277 Dutch patients with this defect found an 8.3% incidence of venous thrombotic complications compared with 2.2% in healthy controls (17).

Protein S Deficiency: The inheritance of the genetic defect is autosomal-dominant and 3 phenotypes of Protein S deficiency have been established, all of which are associated with change in the functional activity of protein C. In heterozygotes, in which the functional activity is between 15-50% of the norm, thrombotic complications occur. A study was conducted among 122 members of a Swedish family, 44 of whom had a proven genetic defect. The data indicate a low thrombotic risk up to 15 years of age, but upon reaching 30 years of age only 50% had no thrombosis (18).

Antithrombin Deficiency: The genetic defect is inherited in an autosomal dominant manner, and 3 subtypes have been established, 1 and 2 are associated with reduced functional activity, and in 3rd disturbed interaction between antithrombin and heparin has been established. Thrombotic events are rare before puberty, but with aging the risk increases. At the age of 50 years carriers developed such complications in 70% (19). In a study of 2132 patients with thromboembolism in Spain, 12.9% were found to be deficient in anticoagulant proteins - 7.3% protein S, 3.2% protein C, and 0.5% with antithrombin respectively (6). There are known data on the risk of thrombosis depending on the type of defect. In patients with protein S deficiency it is 8.5 times higher than in healthy individuals, in antithrombin type 1 deficiency it is 8.1 times, 7.3 for protein C deficiency, and 2.2 for factor V Leiden (20)

Acquired Thrombophilia Risk Factors: Apart from inherited factors, multiple acquired conditions have also been linked with an increased predisposition towards VTE development, including oral contraceptive use, hormone replacement therapy (HRT), pregnancy and postpartum period. Furthermore, malignancy has been recognized as a significant contributory factor affecting clotting dynamics.

Screening is a method in which tests are applied to detect individuals at increased risk of various diseases, without having complaints or clinical manifestations. If the result is positive, additional tests are followed and preventive actions are taken.

Indications for Thrombophilia Screening: Thrombophilia screening should be considered in specific clinical scenarios, including unprovoked VTE, recurrent VTE, VTE at a young age (<50 years), VTE in unusual sites, and family history of thrombosis (21). In patients with recurrent miscarriages, thrombophilia screening may be warranted to identify underlying causes and guide management decisions (22). However, routine

screening of asymptomatic individuals without a clear indication is not recommended due to limited evidence supporting its clinical utility (23).

Testing Strategies: Several laboratory tests are available for thrombophilia screening, including genetic and acquired markers. The most commonly performed tests include factor V Leiden mutation analysis, prothrombin gene mutation analysis, antithrombin activity, protein C activity, and protein S activity (24). Genetic testing for thrombophilia is usually performed using polymerase chain reaction (PCR) or real-time PCR techniques. Additionally, laboratory tests assessing acquired thrombophilia markers, such as antiphospholipid antibodies, lupus anticoagulant, and anticardiolipin antibodies, may be considered in specific clinical scenarios (25).

Implications for Patient Management: Identifying individuals with thrombophilia can have significant implications for patient management, including the initiation of appropriate thromboprophylaxis, lifestyle modifications, and family screening. Anticoagulant therapy is the cornerstone of management in individuals with thrombophilia and a history of VTE (26). However, the duration and intensity of therapy may vary based on the underlying thrombophilia subtype, clinical context, and individual patient factors. Additionally, counseling regarding lifestyle modifications, such as weight management, regular exercise, smoking cessation, and avoidance of estrogen-containing contraceptives, is crucial to reduce the risk of thrombotic events (27).

CONCLUSION

The general practitioner occupies a central place in the health care systems in most European countries. The specificity of the work of these doctors is related to close contact with patients and detailed information for their risk factors and concomitant diseases, which makes it possible to apply preventive and screening methods in primary care. Knowledge of coagulation disorders is essential for the correct selection of patients to be screened, with the aim of early identification of people at risk of thrombotic complications and initiation of prevention with the aim to reducing morbidity and mortality. Further preventive interventions tailored according to individual need can be implemented promptly if identified earlier via systematic testing protocols or population-wide programs. Thrombophilia screening in general practice should be guided by clear indications to identify individuals at increased risk of thrombotic events. The appropriate use of laboratory tests for thrombophilia, along with clinical assessment and evaluation of risk factors, can aid in the management and prevention of thrombotic complications. However, routine screening of asymptomatic individuals without a clear indication is not recommended. Despite advancements in our understanding regarding genetic and acquired risk factors contributing towards venous blood clots formation there remains considerable unresolved debate surrounding the overall clinical utility, prognostication, predictive value and benefit. Laboratory staff, techs subject, expense, quantity sample collection, timing, interpretation, effective communication, follow-up, preventive interventions, established therapy, clinical decision and influenced cost-benefit considerations still evolving controversy . Future research should focus on better identification of high-risk individuals, with an emphasis on tailored prophylactic measures rather than universal screening. Further research is needed to establish the clinical utility and cost-effectiveness of thrombophilia screening in general practice.

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RESEARCH ARTICLE

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The Turkish Validity and Reliability of the Coronavirus-Related Health Literacy Scale on Health Science Students

ABSTRACT

Objective: Health literacy is one's ability to access, comprehend, appraise, and apply health-related information. Health literacy has become an important topic since the COVID-19 pandemic. This methodological study aimed to adapt the Coronavirus-Related Health Literacy Scale (HLS-COVID-Q22) to Turkish.

Methods: The sample consisted of 539 students of the faculty of health sciences of a university in Turkey. The study was conducted between December 2020 and May 2021. The content validity ratio was calculated for content validity. The construct and concurrent validity, internal consistency reliability, test-retest reliability, and ceiling and floor effects were also determined. A confirmatory factor analysis was performed for construct validity.

Results: The fit indices indicated an adequate fit (χ^2/df: 4.97<5, Comparative Fit Index: 0.996). The composite reliability (>0.70) and Cronbach's alpha values (>0.90) were above acceptable limits. Most students had "adequate health literacy" (71.8%). A quarter of the students had "problematic health literacy" (24.5%). The remaining students had "inadequate health literacy" (3.7%). Students with lower levels of health literacy were more likely to have confusion about coronavirus-related information (p<0.001).

Conclusions: The results of the study show that the Health Literacy Scale Related to COVID-19 - Turkish Version (HLS-COVID-TR), consisting of 22 items, has sufficient reliability, internal and external construct validity. It has been determined that it is a valid and reliable scale for measuring health science students' COVID-19 related health literacy levels. Nearly three quarters of the students have sufficient health literacy level.

Keywords: COVID-19 Pandemic, Health Literacy, Validity, Reliability, University Student.

Sağlık Bilimleri Öğrencilerinde COVID-19 ile İlişkili Sağlık Okuryazarlığı Ölçeğinin Türkçe Geçerlik ve Güvenirlik Çalışması

ÖZET

Amaç: Sağlık okuryazarlığı bireylerin sağlık bilgilerine erişme, anlama, değerlendirme ve uygulama yeteneğidir. Özellikle COVID-19 pandemisinde sağlık okuryazarlığı giderek önem kazanmaya başlamıştır. Bu metodolojik çalışmanın amacı sağlık alanında üniversite öğrencilerinde "COVID-19 ile İlişkili Sağlık Okuryazarlığı Ölçeği"nin (SOY-COVID-Q22) Türkçe'ye uyarlamasının gerçekleştirilmesidir.

Gereç ve Yöntem: Bu metodolojik çalışma Türkiye'de bir üniversitede eğitim gören 539 Sağlık Bilimleri Fakültesi öğrencisi ile yapılmıştır. Çalışma Aralık 2020 – Mayıs 2021 tarihleri arasında yürütülmüştür. Kapsam geçerliliğini değerlendirmek için kapsam geçerlilik oranı hesaplanmıştır. Yapı ve eşzamanlı geçerlilik, iç tutarlılık güvenilirliği, test-tekrar test güvenilirliği ve tavan ve taban etkileri de belirlenmiştir. Yapı geçerliliği için doğrulayıcı faktör analizi yapılmıştır.

Bulgular: Uyum indeksleri yeterli uyumu göstermiştir (χ^2/df: 4.97<5, Karşılaştırmalı uyum indeksi: 0.996). Bileşik güvenilirlik (>0.70) ve Cronbach alfa değerleri (>0.90) kabul edilebilir sınırların üzerinde bulunmuştur. Öğrencilerin çoğunun "yeterli sağlık okuryazarlığı"na (%71,8), katılımcıların dörtte birinin "sorunlu sağlık okuryazarlığı"na (%24,5) sahip olduğu belirlenmiştir. Diğer öğrenciler "yetersiz sağlık okuryazarlığı"na (%3,7) sahiptir. Sağlık okuryazarlığı düzeyi düşük olan öğrencilerin COVID-19 enfeksiyonu ile ilgili bilgiler konusunda kafa karışıklığı yaşama olasılığı daha yüksektir (p<0.001).

Sonuç: Çalışma sonuçları, 22 maddeden oluşan COVID-19 ile İlişkili Sağlık Okuryazarlığı Ölçeği - Türkçe Versiyonunun (SOY-COVID-TR) yeterli güvenilirliğe, iç ve dış yapı geçerliliğine sahip olduğunu göstermektedir. Sağlık bilimleri öğrencilerinin COVID-19 ile ilgili sağlık okuryazarlık düzeylerini ölçmek için geçerli ve güvenilir bir ölçek olduğu belirlenmiştir. Öğrencilerin yaklaşık dörtte üçünün yeterli sağlık okuryazarlık düzeyine sahiptir.

Anahtar Kelimeler: COVID-19 pandemisi, Sağlık okuryazarlığı, Geçerlik, Güvenirlik, Üniversite öğrencileri.

INTRODUCTION

The novel coronavirus disease (SARS-COV-2) has taken hold of the whole world since its onset. Therefore, the World Health Organization (WHO) classified the COVID-19 disease as a "public health emergency" (1). The coronavirus continues to mutate, resulting in the emergence of new variants with high transmissibility. Even the vaccinated must take precautions because we do not know how protective the current vaccines are against variant strains of the virus (2). Therefore, preventive interventions against COVID-19 are important.

Globally, responses to the COVID-19 pandemic should be swift, regular, systematic, and coordinated (3). Policymakers and health authorities emphasize that everybody should be doing their part to help prevent the spread of the virus. Moreover, various platforms constantly feed updates and recommendations regarding the pandemic (4).

Health literacy (HL) is defined as one's ability to access the right sources of information, make sense of it, and put it into practice (4). WHO defines HL as "cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand and use information in ways which promote and maintain good health" (5). People with high HL can manage their health and participate actively in their healthcare (6). It is critical to understand public health recommendations, access information about the pandemic, and take protective measures against the virus (4). However, it is not always easy to access reliable sources of information (3). Therefore, individual and social HL is a must for preventing and managing the pandemic (7). People with high HL can tell reliable information from unreliable information regarding the pandemic. They can also access the right sources of information to make the right health decisions (4). There is a large body of research on HL in different groups (older adults, those with chronic diseases, those who tested positive for COVID-19, college students, etc.) (7-9). Health literacy is related to healthcare institutions, healthcare services, healthcare providers, and society. Therefore, we should determine the HL of both healthcare receivers and providers (10). Healthcare providers start developing HL skills in college. Chesser et al. (11) in 2020 found that almost half the college students had high HL levels, whereas the majority had basic levels of COVID-19 knowledge. Nyugen et al. (8) reported a negative correlation between high HL and fear of COVID-19 among medical students. Health and medical students need comprehensive knowledge to strengthen their patients' autonomy, participation, and self-management abilities (12). No systematic data suggests that undergraduate education helps health students develop HL skills. However, undergraduate students are also at risk during the pandemic (8).

Health literacy is assessed using the Health Literacy Survey European Questionnaire (HLS-EU-Q) (13–17) or other measurement tools (11,18,19) Those instruments measure general HL. On the other hand, the Coronavirus-Related Health Literacy Scale (HLS-COVID-Q22) is a more sensitive instrument that measures coronavirus-related HL. The scale was developed for a German population and adapted to Taiwanese and Indonesian populations (20,21).

This study aimed to adapt the HLS-COVID-22 to Turkish. The sample consisted of health sciences students because they will work as healthcare professionals after graduation.

MATERIAL AND METHODS

Ethic Approval and Recruitment: The study was approved by the Ethics Committee of the University (Date:08.10.2020, No:34) and the Faculty of Health Sciences of the University (Date:22.10.2020, No: 27139605-299-E.34413). The study was also registered to the "COVID-19 Scientific Research Platform" of the Turkish Ministry of Health (Date: 30.09.2020). Authorization was obtained from the developer of the HLS-COVID-Q22. Each research stage was carried out according to the ethical principles outlined by the World Medical Association's Declaration of Helsinki. The data collection tools were prepared on Google Forms. All students were informed about the research purpose and procedure. Those who volunteered for the study clicked the "I agree to participate in the study" tab and then filled out the data collection forms.

Participants: This methodological study was conducted between December 2020 and May 2021. The sample consisted of 539 students from the faculty of health sciences of a public university in Ankara, Turkey. The faculty consists of the departments of nutrition and dietetics (n= 170), nursing (n= 149), social work (n= 48), sports sciences (n= 41), speech and language therapy (n=30), audiology (n= 29), child development (n= 28), health management (n= 24), and physiotherapy and rehabilitation (n= 20). The faculty has 2401 students, 688 of whom agreed to participate in the validity stage of the present study. One hundred and forty-nine students were excluded from the analysis because they responded "I do not know" to at least one item. The sample was large enough (n=539) to detect significant differences (22). The intraclass correlation coefficient (ICC) was calculated on 143 students. According to the ICC (>0.90), the minimum number of students was 68 (90% power and 0.05 alpha) (23). The test-retest reliability was assessed on 143 students (Figure 1).

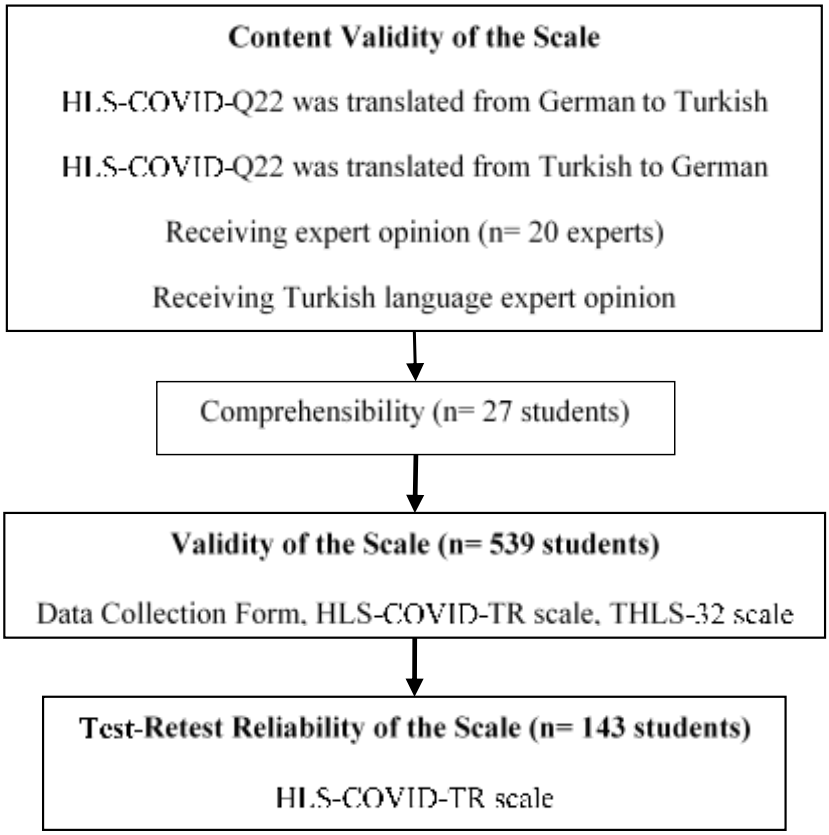

Figure 1. Flow chart.

Data Collection: The data was gathered using the "descriptive questionnaire", Coronavirus-Related Health Literacy Scale (HLS-COVID-Q22) and Turkish Health Literacy Scale (THLS-32).

Descriptive Questionnaire: The descriptive questionnaire was based on a literature (8,11,24,25) review conducted by the researchers. The questionnaire consisted of items on sociodemographic and COVID-19-related characteristics.

Coronavirus-Related Health Literacy Scale (HLS-COVID-Q22): HLS-COVID-Q22 was developed by Okan et al. (25) for a German adult population. The scale consists of 22 items and four subscales: access (six items), understand (six items), appraise (five items), and apply (five items). The items are rated on a four-point Likert-type scale ("1= very difficult" to "4 = very easy"). A mean score of ≤2.5 indicates "inadequate HL." A mean score of >2.5–<3 indicates "problematic HL." A mean score of ≥3 indicates "sufficient HL." The questionnaire has a Cronbach's alpha of 0.94 (25).

Turkish Health Literacy Scale (THLS-32): THLS-32 was adapted to Turkish by Okyay and Abacıgil (26). It was used to check the external validity of the HLS-COVID-TR. It has a conceptual model developed by the HLS-EU consortium. It consists of 32 items rated on a five-point Likert-type scale. It has two subscales [(i) healthcare and (ii) disease prevention and health promotion] and four information processing stages [(i) access, (ii) understand, (iii) appraise, and (iv) apply]. The THLS-32 score is converted using the equation of [(mean of original response format [1-4] - 1)*(50/3)]. The total score ranges from 0 (lowest HL) to 50 (highest HL). The total score is assessed on four levels ("0-25 = inadequate HL," "26-33 = problematic/limited HL," "34-42 = adequate HL," "43-50 = excellent HL"). The THLS-32 has a Cronbach's alpha of 0.92 (26).

Procedure

Content validity: Four linguists were involved in the translation of the HLS-COVID-Q22 into Turkish. In the first stage, two independent Turkish translators who speak and write both Turkish and German very well translated the scale into Turkish. In the second stage, two independent translators translated the Turkish version back into German (back-translation). Afterward, a Turkish language expert reviewed the German and Turkish versions of the items, which were then revised based on his feedback. Twenty experts assessed each item's intelligibility/clarity and relevance using a three-point rating scale (1 = relevant, 2 = relevant but needs minor alteration, 3 = not relevant).

Pilot Test: A pilot study was conducted with 27 students to check the items of the HLS-COVID-TR for intelligibility/clarity and relevance. No modifications were made to the items based on

the results. The students in the pilot study were not included in the main study.

Validity: The data were collected online to determine the internal and external validity of the HLS-COVID-TR.

Reliability: One hundred and forty-three students filled out the HLS-COVID-TR again to determine the test-retest reliability of the scale. HLS-COVID-TR was administered to students as a test-retest two weeks later to determine its consistency across time.

Data Analysis: The Shapiro-Wilk test and normality plots were used for normality testing. Frequency (percentage), mean±standard deviation, or median (quartile 1-quartile 3) values were used to summarize the variables. Content validity, internal construct validity, reliability, discriminant validity, convergent validity, and reproducibility were assessed to determine the psychometric properties of the HLS-COVID-TR.

The Content Validity Ratio (CVR) was calculated for each item. The Content Validity Index (CVI) was calculated for the total scale. Twenty experts determined the Critical CVR (CRVc) value. It was 0.50 at the significance level of 0.05 (27). An item had content validity if CVR was higher than CVRc.

A confirmatory factor analysis (CFA) based on the polychoric correlation matrix was conducted to determine the construct validity of the HLS-COVID-TR. Common goodness-of-fit indices [chi-square, root mean square error of approximation (RMSEA), standardized root means square residuals (SRMR), comparative fit index (CFI), Tucker-Lewis index (TLI), and goodness of fit index (GFI)] were used to check the overall fit of the models (28). The Average Variances Extracted (AVE) indicates that items can better reflect the characteristics of each research variable in the model (29). The factors had convergent validity if the AVE was ≥ 0.50. Composite Reliability (CR) tests based on factor loadings were performed to determine model fitness, whose cutoff should be ≥0.7 (29). Cronbach's alpha values were reported. A Cronbach's alpha of >0.90 indicates excellent internal consistency, >0.80 good internal consistency, and >0.70 acceptable internal consistency (30).

The Spearman rho correlation coefficient between the subscales was compared with the squared root of the AVE value for discriminant validity.

The Spearman rho correlation between the HLS-COVID-TR overall (subscale) score and the HL overall (subscale) score was calculated to check for convergent validity. The following classification was used: <0.30 negligible, <0.50 low, <0.70 moderate, <0.90 high, and ≥0.90 very high correlation (31).

The reproducibility (test-retest reliability) of the HLS-COVID-TR was determined using the intraclass correlation coefficient (ICC, two-way mixed model, absolute agreement). An ICC value of > 0.90 indicates excellent reliability (32). The Bland Altman graph was created from the quantile estimations based on order statistics. The 95% CIs for percentiles were calculated based on quantiles of the binomial distribution.

The Mann-Whitney U and Kruskal-Wallis tests were used to compare the distribution of the HLS-COVID-TR overall scores between the categories of the students' other demographic characteristics at a significance level of 0.05. The Dunn's Bonferoni adjustment results were reported for pair-wise comparisons. The categorical data analysis was applied by using the Pearson Chi_square test.

The statistical significance level was set at two-sided $p<0.05$. The data were analyzed using the Statistical Package for Social Sciences (SPSS for Windows, v 21.0, IBM Corp, Armonk, NY, USA) and the following R language (33) packages: the "psych" (34), "lavaan" (35), "semPlot" (36), "ggplot2" (37), "reshape2" (38), "ggh4x" (39), "DescTools" (40), and "ggpubr" (41).

RESULTS

The Psychometric Properties of the HLS-COVID-TR

Content Validity: Twenty experts evaluated the items. Four items (1, 2, 4, and 17) had a content validity ratio (CVR) of zero (0). The other items had a CVR of greater than zero (min=0.10, max=0.90). The total scale had a CVI of 0.51. Thirteen items had a CVR > critical CVR. The experts re-evaluated the items after modifications. The total scale had a CVI of 0.98. All items had a CVR of greater than 0.90

Internal Construct Validity and Reliability: A confirmatory factor analysis was performed to determine the goodness of fit values of the four-factor and second-order models. Figure 2 shows the standardized factor loadings and the goodness of fit indices of the two models. Each model had an χ^2/df of smaller than 5. The other fit indices also satisfied good fitting model criteria (CFI, TLI, GFI >0.95 and RMSEA, RMSR<1.0). There was a significant difference between the two models. The second-order model was acceptable enough to evaluate the coronavirus-related HL construct. Table 1 shows the standardized factor loadings with 95% CI values and the description of the items. The factor loadings between the items and latent factors were higher than 0.75 for all latent factors ($p<0.05$). The overall fit of the second-order model was deemed to be acceptable based on the model fit indices (Figure 2).

Table 1. The description and factor loadings of the HLS-COVID-TR items.

Item and factor	Description	Std Factor Loading* (lower – upper)
Factor 1	**Access**	0.891 (0.865 - 0.918)
Item 1	Obtaining online information about the coronavirus	0.895 (0.867 - 0.922)
Item 2	Obtaining online information regarding the protective behaviors that can help prevent the coronavirus	0.877 (0.845 - 0.909)
Item 3	Obtaining information from newspapers, magazines, or TV about protective behaviors that help prevent the coronavirus	0.751 (0.707 - 0.795)
Item 4	Learning about how to determine whether I have been infected with the coronavirus	0.766 (0.725 - 0.808)
Item 5	Finding information on where to access professional help in the event of a coronavirus infection	0.856 (0.823 - 0.888)
Item 6	Obtaining information on how much at risk I am for contracting the coronavirus	0.841 (0.804 - 0.877)
Factor 2	**Understand**	0.923 (0.907 - 0.94)
Item 7	Understanding my doctor's, pharmacist, or nurse's instructions regarding preventive measures against the coronavirus infection	0.889 (0.866 - 0.912)
Item 8	Understanding the authorities' instructions regarding protective measures against the coronavirus infection	0.889 (0.863 - 0.914)
Item 9	Understanding family members' or friends' advice regarding preventive measures against the coronavirus infection	0.881 (0.859 - 0.903)
Item 10	Understanding media information on how to protect myself from the coronavirus infection	0.927 (0.909 - 0.944)
Item 11	Understanding online information about the risks of coronavirus	0.933 (0.918 - 0.948)
Item 12	Understanding information in the newspaper, magazine, or television about the risks of coronavirus	0.878 (0.851 - 0.905)
Factor 3	**Appraise**	0.922 (0.905 - 0.939)
Item 13	Assessing the reliability of media information about the coronavirus and the pandemic	0.771 (0.733 - 0.809)
Item 14	Deciding what behaviors pose a higher risk for contracting the coronavirus	0.901 (0.881 - 0.922)
Item 15	Deciding what protective measures to take to prevent coronavirus infection	0.935 (0.917 - 0.952)
Item 16	Assessing how at risk I am for coronavirus infection	0.870 (0.843 - 0.898)
Item 17	Evaluating whether or not I have been infected with the coronavirus	0.795 (0.757 - 0.832)
Factor 4	**Apply**	0.962 (0.949 - 0.975)
Item 18	Deciding on how to protect myself from coronavirus infection based on information in the media	0.871 (0.845 - 0.897)
Item 19	Following my doctor's or pharmacist's instructions on how to deal with coronavirus infection	0.914 (0.896 - 0.933)
Item 20	Using the information my doctor has given me to decide how to deal with coronavirus infection	0.916 (0.899 - 0.933)
Item 21	Using the information in the media to decide how to deal with coronavirus infection	0.864 (0.839 - 0.889)
Item 22	Acting in a way to avoid infecting others with the coronavirus	0.774 (0.737 - 0.811)

*Std: Standardized (lower – upper): the lower and upper limits of 95% Confidence Interval. *p<0.001 for all factor loadings.*
Measured using a 4-point scale where 1 :very difficult, 2: difficult, 3:easy, 4:very easy.

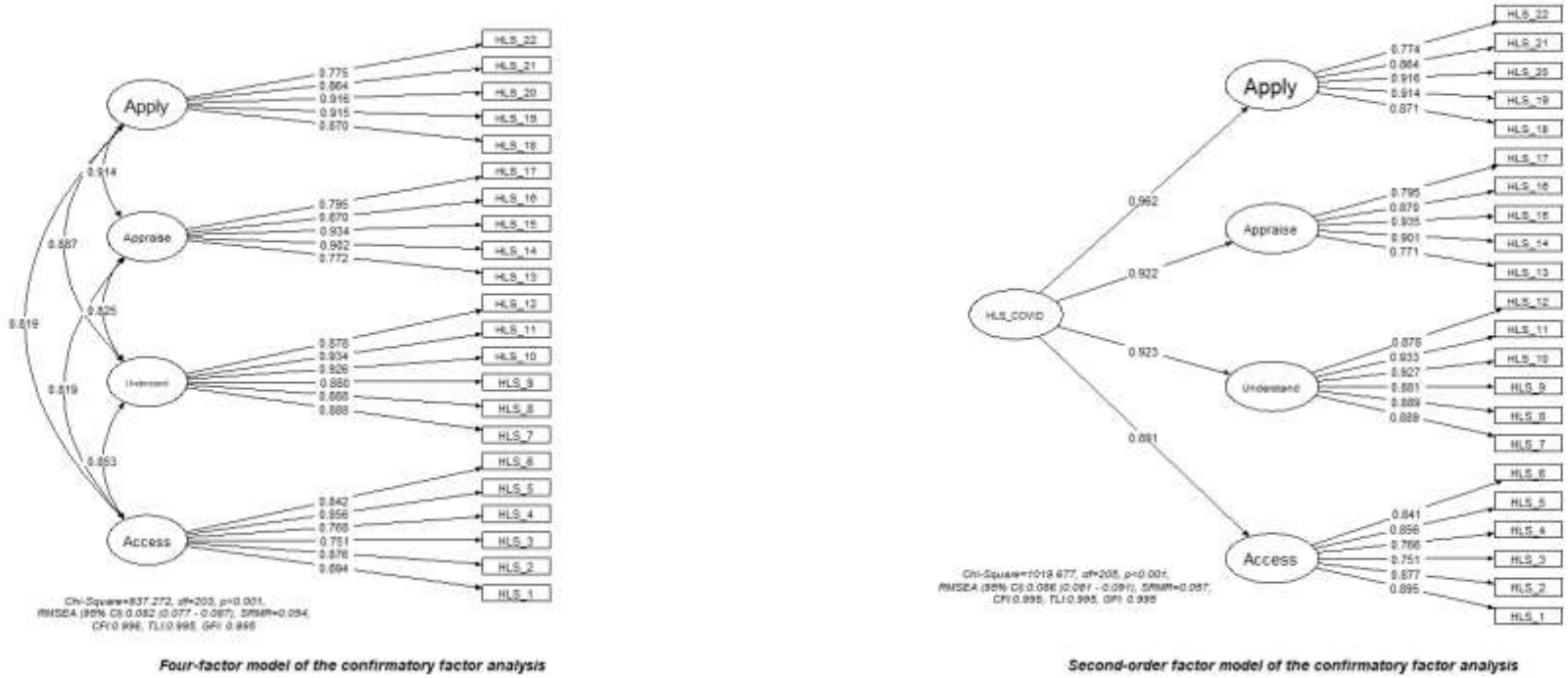

Figure 2. Confirmatory factor analysis results of the four-factor model and second-order factor model. *(df: degree of freedom (χ^2/df: 4.62 for four-factor model and 4.97 for second-order model), RMSEA: Root Mean Square Error of Approximation, CI: Confidence Interval, SRMR: Standardized Root Mean Square Residuals, CFI: Comparative Fit Index, TLI: Tucker-Lewis Index, GFI: Goodness of fit Index)*

Table 2 summarizes the scale reliability measurements and the descriptive statistics of the scores. The composite reliability and AVE values were above the suggested threshold (CR and AVE should be higher than 0.70 and 0.50, respectively). Each subscale had a Cronbach's alpha of greater than 0.90, indicating excellent internal consistency.

Table 2. Reliability test results and descriptive statistics for second-order model confirmatory factor analysis of HLS-COVID-TR.

Factors (items)	CR	AVE	CA (lower - upper)	Median (Q1 – Q3)	Median* (Q1 – Q3)
Access	0.931	0.693	0.914 (0.780 – 0.986)	3.3 (3.0 – 3.8)	38.9 (33.3 – 47.2)
Understand	0.962	0.810	0.957 (0.890 – 0.993)	3.3 (3.0 – 4.0)	38.9 (33.3 – 50.0)
Appraise	0.932	0.734	0.926 (0.794 – 0.991)	3.0 (2.6 – 3.6)	33.3 (26.7 – 43.3)
Apply	0.939	0.756	0.932 (0.812 – 0.992)	3.2 (3.0 – 4.0)	36.7 (33.3 – 50.0)
HLS-COVID-TR	0.959	0.855	0.976 (0.959 – 0.988)	3.2 (3.0 – 3.8)	37.1 (32.6 – 46.2)

*CR: Composite Reliability (>0.70), AVE: Average Variance Extracted (>0.50), CA: Cronbach alpha from Polychoric correlation matrix (>0.90 - excellent), lower-upper: limits of the 95% Confidence Interval, Median (Q1 – Q3): the median value of scale score (quartile 1 – quartile 3), *obtained from transformed scores with the formula [(mean-1)*(50/3)]).*

Discriminant Validity: The square root of the AVE value for each latent construct was higher than the correlation between the related latent construct and other latent constructs (see Table 3).

Table 3. Discriminant validity matrix*

Subscores	Access	Understand	Appraise	Apply
Access	0.832			
Understand	0.757	0.900		
Appraise	0.706	0.693	0.857	
Apply	0.718	0.763	0.793	0.869

**The diagonal values were the* $\sqrt{AVE}$ *for each latent construct. The other values given in columns were the Spearman correlation coefficient between latent constructs.*

External Construct Validity (Convergent Validity). The correlation coefficient between the same subscales was greater than 0.50 (moderate) (see Figure 3). The correlation between the "HL" overall score and the "coronavirus-related HL" overall score was high (rho=0.750).

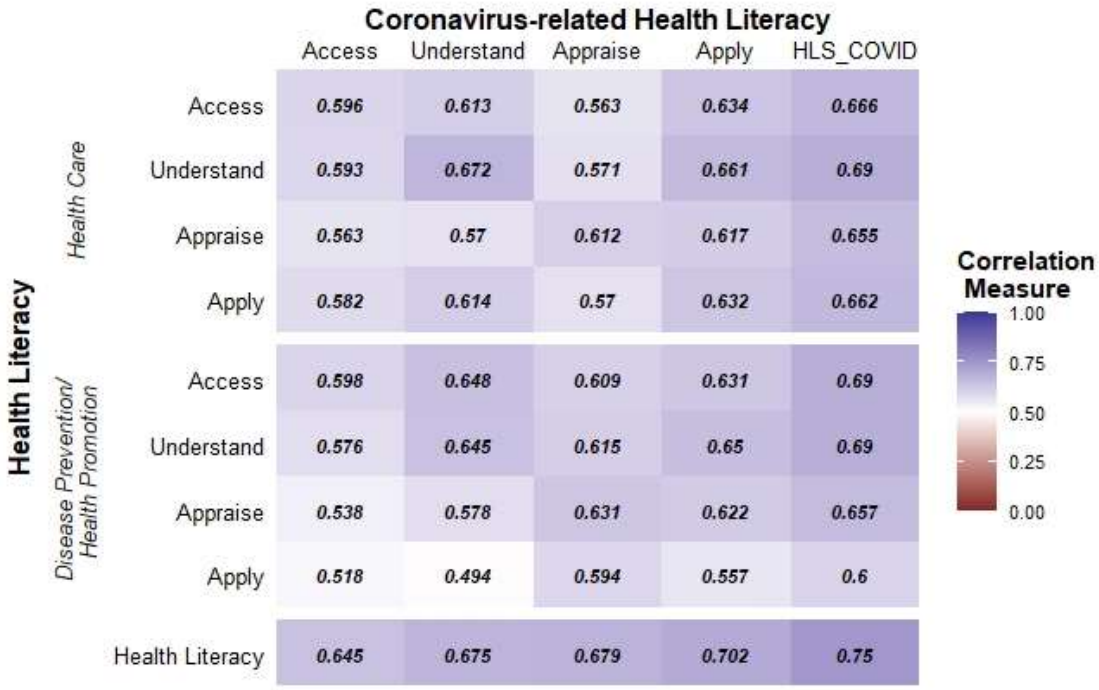

Figure 3. The Spearman rho correlation coefficients between Health Literacy and Coronavirus-Related Health Literacy scale scores. *(all p value<0.05)*

Reproducibility (Test-retest reliability): Figure 4 presents the Bland-Altman graphs showing the difference between the test and retest scores (y-axis) against the mean of the two measurements (x-axis) with ICC values. The HLS-COVID-TR had a test-retest reliability value greater than 0.90 (excellent reliability) and an ICC value of 0.967 (95%CI: 0.961 – 0.972).

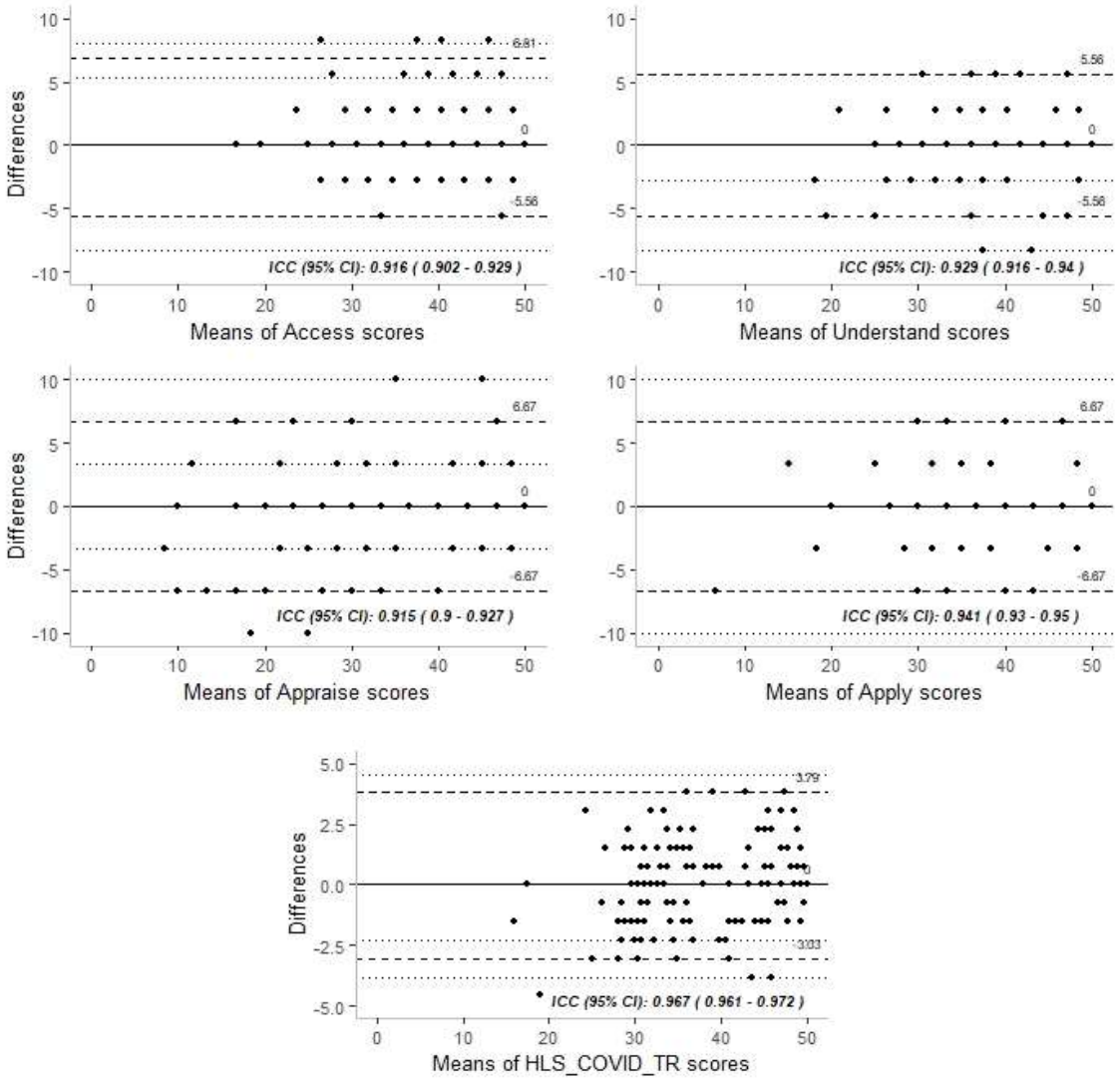

Figure 4. The Bland–Altman plots for the Coronavirus-related Health Literacy (sub)scale test and retest values based on nonparametric quantile estimators. *(The dashed lines represent the nonparametric limits of agreement and median of differences. The dotted lines represent 95% CI based on the binomial distribution)*

Associations Between HLS-COVID-TR Scores and Other Factors: Students had a median age of 20 years (min:18, max:38; Q1:20–Q3:22). Most students were women (86.1%). We used the cutoff values suggested by Okan et al. (25) for the HLS-COVID-TR total score and transformed scores on the transformed metric to mean scores on the original response format. A mean score of ≤2.5 (25.0) indicated inadequate HL. A mean score between >2.5 and <3 (25.0-33.33) indicated problematic HL. A mean score of ≥3 (33.33) indicated sufficient HL. Students had a median HLS-COVID-TR score of 37.1 (Q1:32.6–Q3:46.2). Most students had sufficient HL (71.8%; n=387). A quarter of the students had problematic HL (24.5%; n=132). The remaining students had inadequate HL (3.7%; n=20). Students who were mentally affected by the pandemic had a significantly lower HLS-COVID-TR score (Median:35.6; Q1:31.8–Q3:45.5) than those who were not (Median:38.6; Q1:33.3–Q3:47.0) ($p < 0.05$). Students who knew about the COVID-19 infection very well (Median:50.0; Q1:47–Q3:50) and those who had no confusion regarding the COVID-19 infection (Median:47.7; Q1:36.6–Q3:50) had high HLS-COVID-TR scores ($p < 0.001$) (Table 4). Though not shown in Tables, students who learned about COVID-19 from mass media (n=475; 88.1%), social media (n=442; 82.0%), and the sources of the Ministry of Health (COVID-19 guides and public service ads) (n=408; 75.7%) had sufficient HL (71.6%, 72.2%, and 72.3%, respectively).

Table 4. Demographic characteristics, COVID-19 and coronavirus-related health literacy levels (n=539).

Variables	n (%)	HLS-COVID-TR levels			p*	HLS-COVID-TR scores	p**
		Inadequate	Problematic	Sufficient		Median (Q1-Q3)	
		n (%)	n (%)	n (%)			
HLS-COVID-TR	539 (100.0)	20 (3.7)	132 (24.5)	387 (71.8)	-	37.1 (32.5 - 46.2)	-
Gender							
Female	464 (86.1)	16 (3.4)	118 (25.4)	330 (71.2)	0.361	37.1 (31.8 - 46.2)	0.682
Male	75 (13.9)	4 (5.3)	14 (18.7)	57 (76.0)		36.4 (33.3 - 47.7)	
Grade level (year)							
First	153 (28.4)	5 (3.3)	37 (24.2)	111 (72.5)	0.282	37.1 (32.6 - 45.5)	0.149
Second	152 (28.2)	4 (2.6)	32 (21.1)	116 (76.3)		37.9 (33.3 – 47.0)	
Third	124 (23.0)	7 (5.6)	27 (21.8)	90 (72.6)		37.5 (31.3 - 47.7)	
Fourth	110 (20.4)	4 (3.6)	36 (32.7)	70 (63.6)		34.1 (30.3 - 44.9)	
Mother's education							
Primary education and lower	358 (66.4)	15 (4.2)	92 (25.7)	251 (70.1)	0.590	37.1 (31.8 - 47)	0.994
High school education	116 (21.5)	2 (1.7)	25 (21.6)	89 (76.7)		36.4 (33.3 - 43.9)	
University and higher	65 (12.1)	3 (4.6)	15 (23.1)	47 (72.3)		35.6 (32.2 - 47.3)	
Father's education							
Primary education and lower	245 (45.5)	9 (3.7)	58 (23.7)	178 (72.6)	0.940	36.4 (32.6 - 45.5)	0.831
High school education	142 (26.3)	6 (4.2)	38 (26.8)	98 (69.0)		37.1 (31.8 - 47)	
University and higher	152 (28.2)	5 (3.3)	36 (23.7)	111 (73.0)		36.4 (31.8 - 47)	
Income status perception							
Middle-income status	315 (58.4)	10 (3.2)	81 (25.7)	224 (71.1)	0.236	35.6 (31.8 - 46.2)	0.170
High-income status	95 (17.6)	5 (5.3)	15 (15.8)	75 (78.9)		40.9 (33.3 - 47.7)	
Low-income status	129 (23.9)	5 (3.9)	36 (27.9)	88 (68.2)		35.6 (31.8 - 46.6)	
The impact of the pandemic on life							
Less socialization (Yes)	452 (83.9)	17 (3.8)	117 (25.9)	318 (70.4)	0.217	36.7 (31.8 - 46.2)	0.181
Less physical activity (Yes)	412 (76.4)	16 (3.9)	99 (24.0)	297 (72.1)	0.855	37.9 (32.6 - 47)	0.264
Weight-gain (Yes)	213 (39.5)	7 (3.3)	56 (26.3)	150 (70.4)	0.694	36.4 (31.8 - 47)	0.994
Affecting my mental health							
Yes	295 (54.7)	15 (5.1)	77 (26.1)	203 (68.8)	0.090	35.6 (31.8 - 45.5)	**0.026**
No	244 (45.3)	5 (2.0)	55 (22.5)	184 (75.4)		38.6 (33.3 – 47.0)	
Informed about the COVID-19							
Not well at all	37 (6.9)	1 (2.7)	7 (18.9)	29 (78.4)[a,b]	**0.001**	42.4 (33.3 - 49.2) [a]	**< 0.001**
Not so well	102 (18.9)	5 (4.9)	32 (31.4)	65 (63.7)[b]		35.6 (31.1 - 47.2) [a]	
Undecided	137 (25.4)	11 (8.0)	38 (27.7)	88 (64.2)[b]		34.1 (29.9 - 43.2) [b]	
Well	236 (43.8)	3 (1.3)	54 (22.9)	179 (75.8)[a,b]		37.1 (33.3 - 46) [a]	
Very well	27 (5.0)	0 (0.0)	1 (3.7)	26 (96.3)[a]		50 (47 - 50) [a]	
Confused about COVID-19 information							
Yes, "very confused."	45 (8.4)	3 (6.7)	7 (15.6)	35 (77.8)[a,b,c]	**< 0.001**	37.1 (33.3 - 47) [a]	**< 0.001**
Yes, "somewhat confused."	232 (43.0)	12 (5.2)	81 (34.9)	139 (59.9)[c]		33.3 (30.3 - 41.7) [a]	
No, "barely confused."	194 (36.0)	4 (2.1)	40 (20.6)	150 (77.3)[b]		39.8 (33.3 - 47) [a]	
Not confused at all	68 (12.6)	1 (1.5)	4 (5.9)	63 (92.6)[a]		47.7 (36.6 - 50) [b]	

Data were expressed as frequency and percentage or median (quartile 1- quartile 3). The transformed scores (0-50) with the formula [(mean of original response format [1-4] - 1)(50/3)]) was used for the HLS-COVID-TR overall scores' descriptive statistics. When the mean score was "≤25," ">25.0 -<33.33," and "≥33.33," the health literacy levels were determined as "inadequate health literacy," "problematic health literacy," and "sufficient health literacy," respectively.*

**p-value was obtained from the Chi_square Pearson test for categorical comparisons.*

***p-value was obtained from the Mann-Whitney U test for variables with two categories or the Kruskal-Wallis test for variables with more than two categories. Bold face p-value<0.05.*

[a,b] The groups shown by different letters were different with respect to HLS-COVID-TR overall scores/percentages.

DISCUSSION

The current COVID-19 pandemic caused by SARS-CoV-2 is associated with high mortality and morbidity. Almost all countries have allocated new ad hoc budgets and human power to health services to combat the pandemic (42). Low health literacy is associated with increased healthcare costs (10). Therefore, strategies for preventing COVID-19 are of paramount significance. Today, people can use the Internet and other applications to get information, which is rapidly accessible when and where needed. However, online users sometimes have difficulty accessing accurate and reliable information (4). This is also true for undergraduate students as they are bombarded with misinformation about the pandemic. They are also considered an at-risk group for COVID-19 (8). Therefore, they should be aware of infodemic and be able to access the right information and put it into practice. Some instruments measure general HL, but none focus on coronavirus-related HL. Okan et al. (25) developed the HLS-COVID-Q22

to measure the coronavirus-related HL of a German population aged > 15 years.

In the present study, the HLS-COVID-TR had the same items (n=22) and subscales (access, understand, appraise, and apply) as the original version. This result shows that the terminology of the THLS-32 and HLS-COVID-Q22 is consistent with the HLS-EU-Q. The CFA also revealed that the HLS-COVID-TR had the same factor structure as the original version. Each subscale of the HLS-COVID-TR had an internal consistency of higher than 0.90. The four subscales of the HLS-COVID-Q22 also have high internal consistency (access= 0.891; understand= 0.923; appraise= 0.922; apply= 0.962). The subscales of the HLS-COVID-TR had higher internal consistency values than those reported by Okan et al. (25). This result indicates that the HLS-COVID-TR can be used to measure health science students' coronavirus-related HL.

Almost three-quarters of the students had "sufficient HL" (71.8%), while a quarter of the students had "problematic HL" (24.5%). Okan et al. (25) reported that almost half the students had "sufficient HL." The high health literacy levels in the present study may be because the sample consisted of health science students. Adapting the HLS-COVID-TR to health science students can help healthcare professionals access the right information about COVID-19 and put it into practice.

Students who stated that they knew about COVID-19 very well had high HLS-COVID-TR scores, indicating sufficient HL. It is also noteworthy that students who had high HLS-COVID-TR scores were affected by infodemic the least. Papagiannis et al. (24) determined that almost nine in ten healthcare professionals had a good knowledge of COVID-19. The researchers also pointed out that the healthcare professionals with high knowledge scores had more positive attitudes towards preventive measures. Chung et al. (43) argue that we should focus on strategies that promote well-known hygiene practices and infection-specific HL during the COVID-19 pandemic. Okan et al. (25) found that adults with low HL experienced more confusion, which is consistent with our results. People who access the right information and use it properly have more positive health attitudes.

The COVID-19 pandemic has affected every sphere of social life, such as physical activities, sleep patterns, eating habits, and mental health. The pandemic has impacted college students significantly (16, 44, 45). Our students who were adversely affected by the pandemic had lower HL levels than those who were not. Peksoy-Kaya and Kaplan (16) also reported that almost half the nursing students were adversely affected by the pandemic. Nguyen et al. (7) argue that HL can be a protective factor on mental health and quality of life in people who have tested positive for

CONCLUSION

The HLS-COVID-TR has the necessary psychometric properties for college students in Turkey. This study administered the scale to health science students because they will be working in healthcare institutions and providing care for people who have tested positive for COVID-19. After graduation, health science students will be responsible for accessing and conveying the right information, taking preventive measures, and being role models for society. Therefore, we can use the HLS-COVID-TR to assess students' coronavirus-related HL skills. In this way, colleges can revise their curricula and design interventions to help students with inadequate/problematic HL.

The scale consists of 22 items and four subscales (access, understand, appraise, apply). The items are rated on a four-point Likert-type scale. A mean score of ≤2.5 indicates "inadequate HL." A mean score of >2.5–<3 indicates "problematic HL." A mean score of ≥3 indicates "sufficient HL."

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Conflict of Interest: The authors declare no conflicts of interest.

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RESEARCH ARTICLE

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An MRI Analysis of the Lumbar Lordosis Angle and Lumbar Muscle Thicknesses in Patients with Non-Specific Low Back Pain

ABSTRACT

Objective: This study aimed to examine the relationship of lumbar lordosis angle and lumbar muscle thickness with non-specific low back pain (LBP) through magnetic resonance imaging (MRI) images.

Methods: The study included 96 individuals (43 men/53 women) aged between 18-65 with non-specific LBP that is not explained by disc pathology based on MRI, who applied to affiliated Training and Research Hospital with the complaint of LBP between March-June 2019. Sociodemographic information was recorded using an LBP assessment form. The Oswestry LBP Disability Questionnaire was used for LBP disability. The thicknesses of muscle (m.) psoas major, m. multifidus, m. quadratus lumborum and m. erector spinae were measured corresponding to the L3-L4 vertebral level by using Radiant DICOM viewer program. The Cobb Angle method was used for lumbar lordosis angle determination. Measurements were made in three repetitions using the Radiant DICOM viewer program.

Results: The results showed that an inverse relationship was found between the Oswestry Disability Index (ODI) and m. psoas major thickness ($p<0.05$). Given the comparison of right-left side muscle thicknesses, left side muscles were thicker ($p<0.05$). There were no significant differences observed between males and females in terms of lumbar lordosis angle (LLA). However, in terms of muscle thickness, males exhibited higher values, except for the transverse measurements of the right quadratus lumborum and left erector spinae muscles, which showed no significant differences ($p < 0.05$). Furthermore, a positive correlation was found between LLA and the transverse thickness of the left psoas major muscle ($p = 0.034$) and the anterior-posterior thickness of the bilateral erector spinae muscles ($p < 0.001$).

Conclusions: In regard to inverse relationship between m. psoas major thickness and ODI, m. psoas major should be taken into consideration to alleviate the disability caused by LBP. Additionally, the difference on both sides is likely one of the causes of muscle imbalance, and this might be one of the reasons for LBP, thereby causing disability in daily tasks due to LBP.

Keywords: Low Back Pain, Muscle Thickness, Spinal Curvatures, Lordosis Angle, Magnetic Resonance Imaging, Cobb Angle.

Non-Spesifik Bel Ağrılı Hastalarda Lumbal Lordoz Açısı ve Lumbal Kas Kalınlıklarının MRG Analizi

ÖZET

Amaç: Bu çalışmada lomber lordoz açısı ve lomber kas kalınlığı ile non-spesifik bel ağrısı arasındaki ilişkinin manyetik rezonans görüntüleme (MRG) görüntüleri aracılığıyla incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya bel ağrısı şikayetiyle ilgili Eğitim ve Araştırma Hastanesine başvuran, MRG ile disk patolojisi ile açıklanamayan non-spesifik bel ağrısı olan, 18-65 yaş aralığındaki, 96 birey (43 erkek/53 kadın) dahil edildi. Sosyodemografik bilgiler bel ağrısı değerlendirme formu kullanılarak kaydedildi. Bel ağrısı engellilik düzeyi, Oswestry Bel Ağrısı Engellilik Anketi (ODI) ile değerlendirildi. L3-L4 vertebra seviyesine karşılık gelen musculus (m.) psoas major, m. multifidus, m. quadratus lumborum ve m. erector spinae'nın kalınlıkları ölçüldü. Lomber lordoz açısının belirlenmesinde Cobb açı ölçme yöntemi kullanıldı. Tüm ölçümler Radiant DICOM görüntüleme programı kullanılarak üç tekrarlı olarak yapıldı.

Bulgular: Elde edilen sonuçlar, ODI ile m. psoas major kalınlığı arasında ters bir ilişki bulunduğunu gösterdi ($p<0.05$). Sağ-sol taraf kas kalınlıkları karşılaştırıldığında, sol taraf kasların daha kalın olduğu görüldü ($p<0.05$). Lumbal lordoz açısı (LLA) bakımından cinsiyetler arasında istatistiksel bir fark bulunmazken, sağ m. quadratus lumborum ve sol m. erector spinae transvers ölçümleri dışında erkeklerde kas kalınlıkları daha yüksekti ($p<0.05$). Ayrıca, LLA, sol taraf m. psoas major transvers kalınlığı ($p =0.034$) ve bilateral anterior-posterior m. erector spinae kalınlığı ($p <0.0001$) ile pozitif yönlü ilişkiliydi.

Sonuç: Çalışma sonucunda ortaya çıkan m. psoas major kalınlığı ve ODI arasındaki ters ilişki, bel ağrısından kaynaklanan engelliliği azaltmada bu kasın da göz önünde bulundurulması gerektiğini göstermiştir. Ayrıca, her iki taraf kas kalınlıkları arasındaki fark, kas imbalansına neden olmuş olabilir, bu durum bel ağrısına yol açmış ve dolayısıyla günlük hayatta karşılaşılan engelliliğe neden olmuş olabilir.

Anahtar Kelimeler: Bel Ağrısı, Kas Kalınlığı, Omurga Eğrilikleri, Lordoz Açısı, Manyetik Rezonans Görüntüleme, Cobb Açısı

INTRODUCTION

Low back pain (LBP) is not only a widespread symptom, but it is also a significant public health problem that affects all civilizations and leads to lost productivity and economic losses due to functional restrictions (1–3). Moreover, LBP may also be highly prevalent due to the fact that it can affect adults of any age range (1,2). The worldwide point prevalence of LBP was shown to be 9.4% in a study by Damian Hoy et al. (2014). The results of Vos et al.'s study displayed that LBP point prevalence was found to be 7.3%, corresponding to 540 million people in the general population (4). Despite being widespread and having a high prevalence, the pathology that causes LBP in 85% of the patients cannot be determined clearly (5).

LBP can be caused by aberrant adaptations in the biomechanics of the lumbar region. The mechanical alterations in this region are able to change the traction angles of the muscles and thus affect the spine alignment; thereby, the altered body pattern might indirectly cause symptoms (6). Curvatures, one of the most important features of the spine biomechanics, provide optimal energy expenditure and movement capacity (7,8). Changes in curvatures such as loss or increase of lumbar lordosis might have an effect on muscle functions, range of motion and mobility by altering the biomechanical structure (7,8). Regarding muscular components of the region, the stabilization role of m. erector spinae and m. multifidus plays a significant role in the protection of the LLA, and maintaining normal movement capacity and stabilization with the help of these muscles may reduce the risk of LBP (9,10). In addition to these muscles, the m. psoas major and m. quadratus lumborum act synergistically with the deep back muscles in the body to gain upright posture (10).

Various studies on LBP have been conducted as to whether changing lumbar muscle thickness (LMT) and LLA cause LBP. Studies on LBP in the literature generally focused on the erector spinae and multifidus, and when comparing the thickness of the muscles, the results were mostly given by taking the average of both sides without comparison between the left and right sides (11–14). Additionally, there is a lack of studies examining the relationship between LLA and muscle thickness (15–17).

Looking at studies investigating the relationship between LBP and LLA, an association was found between LLA and LBP in a meta-analysis (8), while another study found no relationship between these two variables (18). A similar picture is seen in studies examining the correlation between LBP and LMT. Wallwork et al. (19) emphasised that alteration on LMT would be related to LBP, while Masaki et al. (20) came to the opposite conclusion. As is seen, the results of studies that investigated the relationship between LMT or LLA on LBP in the literature have discrepancies and have not reached a consensus.

The aim of this study was to determine the relationship of LLA and LMT with non-specific LBP through MRI images and to introduce a new perspective in addition to existing studies.

MATERIAL AND METHODS

Participants: This cross-sectional study included 43 males and 53 females with non-specific LBP, who applied to the Radiology Department of the authors' affiliated hospital between April-June 2019. The necessary permission for the study was obtained from the Non-Invasive Clinical Research Ethics Committee of the Rectorate of the authors' affiliated institutions. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The individuals who met the inclusion criteria were informed and the consent was obtained about the study.

During the data collection process of the study, patients who applied to the Radiology Department of the University Hospital with the complaint of LBP were asked to participate in the study. The participants of the current study were selected based on the purposive sampling method. A total number of 180 individuals was taken in the study for two weeks data collections term. According to our inclusion and exclusion criteria, 96 individuals were eligible to participate in the study. Prior to the data analysis, the following participant selection criteria were applied.

The inclusion criteria were determined as being aged between 18-65 years old, having non-specific LBP that is not explained by disc pathology, and volunteering to participate. To ensure participants had non-specific LBP, an experienced radiologist investigated the MRI of patients to omit participants who had pathological signs that would cause symptomatic low back pain. In addition, in the given LBP assessment form, participants were asked whether they had any other pathology, symptoms, or radiating pain. Individuals were excluded if there was the presence of any bone, muscular, or disc pathology causing LBP in the lumbar region (as seen on an MRI by an experienced radiologist), if they had any misalignments, such as scoliosis, by observing MRIs on the front view, or if they had undergone any previous operation on the lumbar region. Sociodemographic data, physical condition information, surgical status related to the lumbar region, trauma history, and pain duration of the individuals were questioned using the LBP assessment form prepared by us. The individual's height and weight were recorded in metres (m) and

kilograms (kg). With these data obtained, body mass index (BMI) was calculated by dividing the individual's weight by the square of his height.

Outcome Measures

Low Back Pain Questionnaire: The Turkish version of Oswestry LBP Disability Questionnaire v2.0 was used to evaluate LBP disability (21). In this survey, there are 10 parameter titles: pain intensity, personal care, lifting, walking, sitting, standing, sleep, sexual life, social life, and travel. Numbers from 0 to 5 next to each answer qualify the score of that answer. For the questions given different answers for the same question, the option with the highest score among the given answers was chosen to reckon. ODI score as a percentage was obtained from the results.

MRI Analysis: Participants were taken into an MRI device in the supine position, and the MRI procedure was implemented with 1.5 T systems (GE Medical Systems, USA; Siemens Healthcare, Erlangen, Germany). All MRI measurements were made by an expert radiologist. MRI of the individuals was taken from the archives of the Radiology Department of the hospital. LMT and LLA measurements were evaluated on the Digital Imaging and Communications in Medicine (DICOM) imaging and processing program (Radiant DICOM Viewer 4.6.9) in three repetitions. The arithmetic averages of the values were recorded.

The COBB angle method was used to evaluate the LLA in the sagittal plane. It was determined by looking at the angle between the vertebrae forming the LLA (superior L1 endplate and inferior L5 endplate). A line was drawn parallel to the upper edge of the L1 vertebral body, which is the top vertebra involved in the curvature. Next, a line was drawn parallel to inferior L5 endplate, the last vertebra of the lumbar curve. The angle between the two linear lines drawn was measured (Fig. 1). Each measurement was repeated three times by an experienced radiologist and averages of those were recorded as degree values.

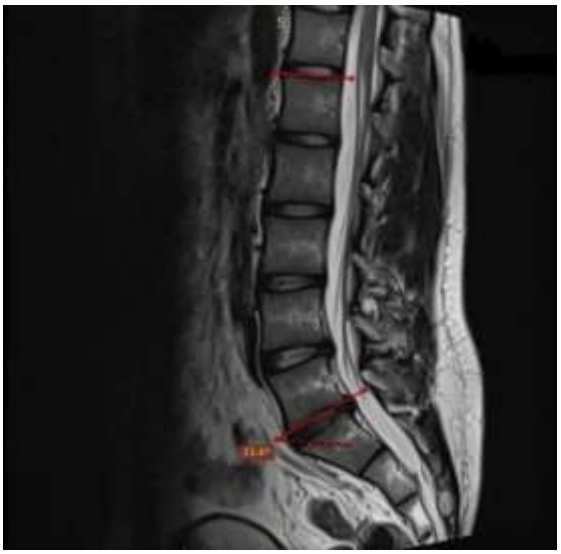

Figure 1. LLA Measurement According to COBB Angle Method (The degree between L1 and L5)

The thickness of the m. psoas major, m. multifidus, m. quadratus lumborum and m. erector spinae muscles were measured on the horizontal plane corresponding to the L3-L4 level in the sagittal plane (Fig. 2a). Since m. multifidus and m. erector spinae muscles could not be clearly distinguished from each other on the MRI, they were considered as a whole and recorded as m. erector spinae. Bilaterally, the thickest parts of the muscles were measured anterior-posterior and transverse and recorded in millimetres (mm) (Fig. 2b).

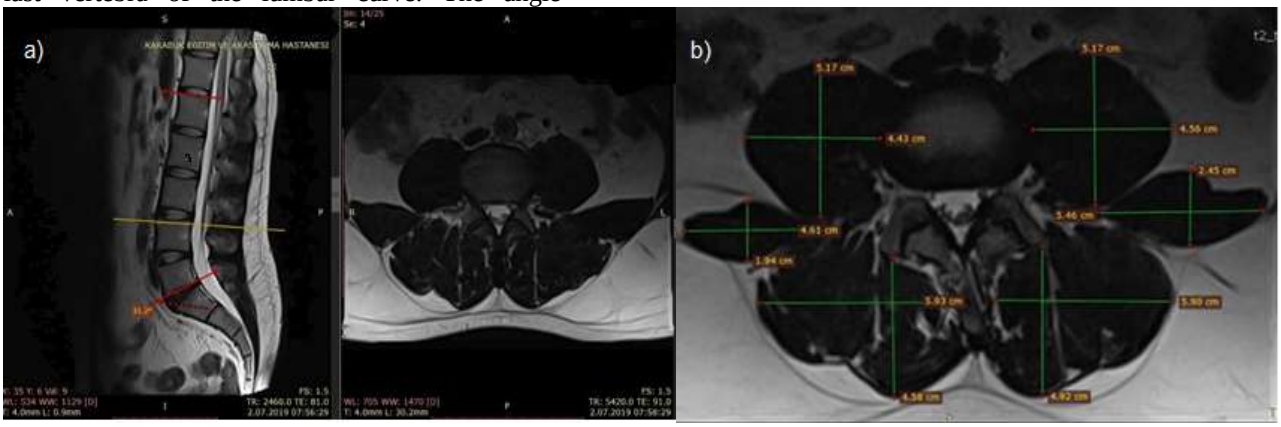

Figure 2. Muscle Thickness Measurement with MRI Imaging: a) T2W determination of L3-L4 level in sagittal and axial planes, b) Bilateral muscle thickness measurements

Statistical Analysis: The data were analysed with SPSS 24.0 (SPSS 24 for Windows, Armonk, NY: IBM Corp) package program. Descriptive values were expressed as mean, standard deviation (SD), number and percentage frequencies depending on the variable type. The compatibility of numerical properties to normal distribution was examined using the Shapiro Wilk test. Mann Whitney U test was performed in comparison of ODI, age, the anterior-posterior thickness of bilateral m. quadratus lumborum and right-side m. psoas major, and transverse thickness

of left-side m. erector spinae. BMI, LLA, anterior-posterior thickness of bilateral m. erector spinae and left-side m. psoas major, the transverse thickness of bilateral m. quadratus lumborum, m. psoas major and right-side m. erector spinae differences were analysed with independent samples t test. The relationships between continuous variables were analysed using the Spearman correlation coefficient, and differences between categorical variables were analysed using the Pearson chi-square analysis. The correlation was classified as strong (r≥0.70), moderate (r≥0.40 or r<0.70) or weak (r<0.40), adopting a 95% confidence interval (22). A post-hoc power analysis was performed using an alpha value of 0.005. P<0.05 was accepted as the statistical significance level.

RESULTS

The participants' characteristics are illustrated in Table 1, while information of muscle thickness is shown in Table 2. Age, BMI, and LLA values were similar; therefore, participants displayed a homogeneous distribution regarding these parameters. The ODI score of females was determined to be higher than that of males in relation to gender (p <0.05).

Table 1. Characteristics of Patients

	Females (n=53)	Males (n=43)		Total (n=96)
	mean± SD	mean ± SD	p^{β}	mean ± SD
Age (year)	37.62 ± 10.62	38.72 ± 12.91	0.704	38.11 ± 11.65
BMI (kg/m^2)	26.69 ± 5.36	26.48 ± 3.72	0.826	26.59 ± 4.68
ODI (%)	35.94 ± 16.79	25.44 ± 16.12	0.003*	31.24 ± 17.22
LLA (º)	34.52º ± 11.33º	32.94º ± 12.15º	0.512	33.83º± 11.67º

*p<0.05, Values express as Mean ± Standard Deviation, BMI: Body Mass Index, ODI: Oswestry Disability Index, LLA: Lumbar Lordosis Angle, β: Mann Whitney U test and Independent sample t-test

The differences between the right and left side muscle thickness of the anterior-posterior m. quadratus lumborum and m. psoas major were statistically significant (p <0.05). It was determined that the difference between right and left transverse thicknesses was significant (p <0.05) (Table 2). As to LMT between gender, a significant difference was identified as higher in males except for right m. quadratus lumborum and left m. erector spinae transverse measurements (p <0.05) (Table 3).

Table 2. The Comparison of Individuals' Muscle Thicknesses According to Left and Right Sides

	Individuals (n=96) mean ± SD					
	Anterior-Posterior			Transverse		
	Right	Left	p^{β}	Right	Left	p^{β}
M. quadratus lumborum	20.53 ± 6.72	21.40 ± 6.08	0.014*	48.34 ± 7.59	50.81 ± 7.72	<0.001*
M. erector spinae	56.33 ± 6.75	56.69 ± 6.92	0.062	65.56 ± 6.78	66.69 ± 6.46	0.009*
M. psoas major	41.58 ± 6.42	42.34 ± 6.07	0.048*	33.71 ± 6.65	32.54 ± 6.58	0.009*

*p<0.05, Values express as Mean ± Standard Deviation, β: Independent sample t-test

Table 3. The Comparison of Muscle Thickness According to Genders

			Females (n=53)	Males (n=43)	
			mean ± SD	mean ± SD	P^{β}
TRANSVERSE	Right	M. quadratus lumborum	47.02 ± 7.39	49.96 ± 7.61	0.59
		M. erector spinae	63.05 ± 6.24	68.65 ± 6.17	<0.001*
		M. psoas major	30.20 ± 5.94	38.04 ± 4.64	<0.001*
	Left	M. quadratus lumborum	47.82 ± 7.37	54.49 ± 6.51	<0.001*
		M. erector spinae	65.40 ± 6.10	68.28 ± 6.60	0.05
		M. psoas major	29.09 ± 5.42	36.80 ± 5.15	<0.001*
ANTERIOR POSTERIOR	Right	M. quadratus lumborum	16.33 ± 4.35	25.70 ± 5.40	<0.001*
		M. erector spinae	52.62 ± 5.76	60.89 ± 4.81	<0.001*
		M. psoas major	37.27 ± 3.76	46.91 ± 4.82	<0.001*
	Left	M. quadratus lumborum	17.74 ± 3.88	25.90 ± 5.23	<0.001*
		M. erector spinae	52.71 ± 5.58	61.61 ± 5.01	<0.001*
		M. psoas major	38.39 ± 3.74	47.20 ± 4.70	<0.001*

*p<0.05, Values express as Mean ± Standard Deviation, β: Mann Whitney U test and Independent sample t-test

While there was no relationship between the ODI and age, BMI, or LLA, an inverse relationship was observed between the ODI and both sides anterior-posterior and the left side transverse m. psoas major thickness (Table 4). A relationship was found between LLA and BMI ($p < 0.05$). Regarding the relation between LLA and muscle thickness, a relationship was determined between bilateral m. erector spinae anterior-posterior and left-sided m. psoas major transverse thicknesses ($p < 0.05$) (Table 4).

Table 4 The Relationship between LLA, ODI and LMT

			Individuals (n=96)			
			LLA		ODI	
			r	**p**	**r**	**p**
ANTERIOR POSTERIOR	**Right**	M. quadratus lumborum	0.145	0.160	-0.164	0.110
		M. erector spinae	0.391	<0.001*	-0.093	0.366
		M. psoas major	-0.129	0.210	-0.251	0.014*
	Left	M. quadratus lumborum	0.131	0.204	-0.151	0.142
		M. erector spinae	0.381	<0.001*	-0.104	0.315
		M. psoas major	-0.110	0.286	-0.222	0.030*
TRANSVERSE	**Right**	M. quadratus lumborum	0.010	0.923	-0.126	0.221
		M. erector spinae	-0.107	0.297	-0.049	0.638
		M. psoas major	0.133	0.195	-0.153	0.136
	Left	M. quadratus lumborum	0.081	0.434	-0.148	0.150
		M. erector spinae	-0.111	0.283	-0.034	0.741
		M. psoas major	0.217	0.034*	-0.285	0.005*

*p<0.05, r: Pearson correlation coefficient, ODI: Oswestry Disability Index, LLA: Lumbar Lordosis Angle

A post hoc power analysis for the difference between muscle thickness (left and right sides) demonstrated 87% of power with 96 side matched pairs, with an effect size of $d = 0.32$ ($\alpha = 0.05$).

DISCUSSION

In the present study, the relationship of LLA and LMT with LBP was investigated through the analysis of parameters related to muscles and spinal alignment on MRI. The results of the current study emphasise that as m. psoas major thickness increased, disability score decreased in individuals with LBP. In addition, this study also revealed imbalanced muscle pairs in individuals with LBP and corroborated that females were disabled more than males due to LBP.

Individuals with LBP have overactive muscles during physical activity as their muscles attempt to protect the spine while the body moves. It is presumed that misalignment of lumbar muscles and decreased LMT are associated with LBP (16). A systematic review by ShahAli et al. (23) questioned the relationship between muscle thickness and muscle activity. They reviewed 14 studies that assessed the correlation of muscle thickness and muscle activity with ultrasonography and electromyography on LBP and healthy control individuals. They resulted in a strong correlation between muscle thickness and muscle activation out of five studies. In a study comparing cross-sectional area of lumbar muscles by Singh et al. (13), m. psoas major was atrophic at the level of L3-L4 vertebra, whilst they found no statistically significant result in the cross-sectional area of the m. psoas major. In the other study using MRI to determine the size of lumbar muscles; m. psoas major, m. erector spinae, and m. multifidus were smaller in LBP patients (24). Similarly, the current study revealed an inverse correlation between ODI and both sides of the m. psoas major anterior-posterior and left side m. psoas major transverse thicknesses. It seems that the thickness of m. psoas major, and indirectly the activation of this muscle is essential in individuals with LBP in order to maintain optimal biomechanics. To relieve LBP, considering the function of the m. psoas major, which is a flexion muscle, flexion movement in this region plays an important role in the biomechanics of LBP.

The findings of current study, which are supported by some studies in the literature (1,25–27), have displayed that ODI was found to be higher in females. A study with 600 participants comparing the associated factors of LBP between genders revealed that the prevalence of LBP in females is higher than in males (1). The result of this study showed the prevalence of LBP in females was nearly two times higher than in males. Another study conducted by Ferrari et al. (27) investigated clinical characteristics of non-specific LBP patients and relationships between disability and gender. They implemented the Roland-Morris disability Questionnaire on 310 outpatients, and the result of this study revealed a significant relationship between disability and being female ($p = 0.018$)(27). Females, therefore, seem to be more restricted in performing daily work activities compared to males (25). Consequently, females might be considered to be in the higher-risk group in terms of having

higher ODI scores and experiencing limitations in daily life activities.

There is a lack of studies comparing both sides of lumbar muscle thickness in the literature (14,20). Although it can be thought that there may be differences in the muscle thickness of two sides depending on the use of the dominant side, comparison of the muscle thickness of both sides may still be important to draw attention to a possible pathology. There is some evidence in the literature that LBP patients showed imbalanced activity of lumbar muscles (12,13,28). Singh et al. (13) investigated the associations between lumbar parameters and LBP by measuring the cross-sectional area of trunk muscles at three levels of the intervertebral disc (L3–L4, L4-L5, and L5–S1). The result of this study was that the right side of the m. multifidus and the left side of the m. erector spinae were larger than those of the other side in LBP patients at the L3-L4 level. Additionally, a recently published study investigating muscle size and symmetry in dancers with LBP found a significant difference between right and left side m. multifidus thickness (29). They concluded that the difference in both side muscle thickness may be attributed to the leg dominance laterality preference of their participants. Similarly, in our study, a significant difference was found in the comparison of both side thicknesses except for the only m. erector spinae anterior-posterior thickness. The authors of the current study deem that this might be most likely due to the preferences of dominance. One of the factors' causing LBP is likely to be the significant difference seen between muscle thicknesses.

Menezes et al. (15), comparing LMT according to gender, emphasised that males had thicker muscles. On the other hand, in another study conducted with LBP patients and the control group, there was no statistically significant difference between genders in terms of thickness of m. paraspinalis, m. psoas major, and m. quadratus lumborum (30). In the current study, all muscle thicknesses, but not the right m. quadratus lumborum and the left m. erector spinae transverse thickness, were significantly different between males and females. Similarly, in a study conducted by Lim (2013), a significant difference was found between gender and thicknesses of m. erector spinae and m. multifidus. The result of Lim's study that males had significantly greater muscle mass than females supports the result in this study (9). One of the reasons of having thicker muscle may be that males have mostly greater BMI than females. In the current study, a positive relationship was found with BMI in the majority of LMT. As BMI increased, muscle size increased, and LMT of males was thicker than females. The relationship between LMT and BMI in this study is consistent with previous studies (9,15), implying a significant relationship between muscle size and BMI of individuals.

The relationships between LLA and LBP have shown diversity in previous studies (7,8). While Cho et al. (7) report that LLA is associated with LBP, Chun et al. (8) point out that LLA was lower in individuals with LBP compared to healthy controls. In this study, it was found that there was no relationship between LLA and ODI scores. In the literature, there is no optimal level for LLA, and it appears in a wide range, and it is affected by age and sex. This is due to the diversity of individual factors, the influence of ethnicity on body biomechanics, and reasons that might arise from the measurement method. These factors could be the reason why there was no relationship between LLA and ODI in this study.

There are studies showing that LLA is related to muscle thickness, especially m. erector spinae and m. multifidus (6,15–17). The results of the current study, which examined the relationship between LLA and bilateral m. erector spinae anterior-posterior and left-sided m. psoas major transverse thickness, support previous studies. Menezes et al. (15) reported that although there was no relationship between m. erector spinae and LLA, a relationship was found between LLA and the thicknesses of m. multifidus and m. psoas major. In addition, Jun et al. (17) emphasised that the thicknesses of m. multifidus and m. erector spinae are also associated with LLA. Individuals with increased LLA have a number of biomechanical adaptations. Also, it is known that the thickness of the muscle biomechanically tends to enlarge when a muscle fibril shortens (6). While the lumbar extensor and hip flexor muscles shorten, the abdominal muscles and hip extensor muscles, which are antagonists, tend to lengthen. This situation is seen as vice versa way in individuals with LLA decrease (31).

This study has some limitations. The study differed from the previous studies in that the healthy control group was not included in this study. In addition, since m. multifidus was difficult to distinguish from m. erector spinae in MRI, the two muscles were measured together and recorded as m. erector spinae. In this context, failure to measure m. multifidus and m. erector spinae independently may have created an obstacle in determining their relationship with LBP.

CONCLUSION

Given the inverse relationship between m. psoas major thickness and LBP disability, we think that m. psoas major, which might be ignored in the treatment of LBP, should be added to both evaluation and rehabilitation programs for optimal recovery. The imbalance of muscles between the right and left sides is another significant factor, and this result should be paid attention to for the treatment of LBP. In this current study, this imbalance was also seen on the m. psoas major, which is a pelvic flexor muscle, not only lumbar extensor muscles. In conclusion, we believe that the

results of the current study would be helpful for clinicians in this field with regard to providing a more effective treatment option for patients.

On the other hand, females might be considered to be more susceptible to LBP-related disability since females had higher ODI scores than males, which means that they may be in the high-risk category for LBP. As in seen our study, females could be informed about for protection their body wellness, and also to be encouraged the participation of the LBP preventing exercise education.

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RESEARCH ARTICLE

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Post-COVID-19 Cardiovascular Disorders and the Molecular Mechanism of NET Formation

ABSTRACT

Objective: The post-COVID-19 process is not completely understood, as it affects COVID-19 survivors at all levels of disease severity, not all of whom are hospitalized. One of the long-lasting COVID-19 symptom categories, cardiovascular disorders (including acute heart failure, palpitations, hypotension, venous thromboembolic diseases, arrhythmias, myocarditis, and increased heart rate), may derive from a systemic inflammatory response to the viral infection. NETs (neutrophil extracellular traps) that fight invading viruses in extracellular cardiac spaces accumulate due to COVID-19, hyperinflammation, and cytokine storms. Our study focuses on cardiovascular disorders as COVID-19 sequelae. To determine the role of NETs in these disorders, we aimed to measure levels of PAD4, MPO, MMP-9, and H3Cit.

Methods: Forty patients with long-term cardiac complications associated with a history of COVID-19 and forty healthy people were included in this study.

Results: We found significant differences in PAD4, H3Cit, and MPO plasma levels between the post-COVID-19 and control groups (p values < 0.05). The expression levels of PAD4 mRNA were lower and MMP-9 mRNA levels were higher in the post-COVID-19 group compared with the control subjects.

Conclusions: These findings suggest that PAD4, MPO, MMP-9, and H3Cit are potential biomarkers of NET dysregulation and may cause post-COVID-19 symptoms, especially cardiovascular disorders.

Keywords: Cardiovascular Abnormalities, Citrullinated Histone H3, Neutrophil Extracellular Traps, Peptidyl Arginine Deiminases 4, Post-Acute COVID-19 Syndrome.

COVID-19 Sonrası Kardiyovasküler Bozukluklar ve NET Oluşumunun Moleküler Mekanizması

ÖZET

Amaç: Tamamı hastaneye yatırılmayan, hastalık şiddetinin her seviyesinde ki COVID-19 mağdurlarını etkilediği için, COVID-19 sonrası süreç tam olarak anlaşılamamıştır. Uzun süreli COVID-19 semptom kategorilerinden biri olan, kardiyovasküler bozukluklar (akut kalp yetmezliği, çarpıntı, hipotansiyon, venöz tromboembolik hastalıklar, aritmiler, miyokardit ve artmış kalp hızı dahil), viral enfeksiyona sistemik bir inflamatuar yanıttan kaynaklanabilir. Hücre dışı kalp boşluklarında istilacı virüslerle savaşan NET'ler (nötrofil hücre dışı tuzakları), COVID-19, hiperinflamasyon ve sitokin fırtınaları nedeniyle birikir. Çalışmamız, COVID-19 sekeli olarak kardiyovasküler bozukluklara odaklanmaktadır. NET'lerin bu bozukluklardaki rolünü belirlemek için PAD4, MPO, MMP-9 ve H3Cit düzeylerini ölçmeyi amaçladık.

Gereç ve Yöntem: COVID-19 öyküsü ile ilişkili uzun süreli kardiyak komplikasyonları olan kırk hasta ve kırk sağlıklı birey, bu çalışmaya dahil edildi.

Bulgular: COVID-19 sonrası ve kontrol grupları arasında PAD4, H3Cit ve MPO plazma seviyelerinde anlamlı farklılıklar bulduk (p< 0.05). PAD4 mRNA ekspresyon seviyeleri, kontrol deneklerine kıyasla COVID-19 sonrası grupta daha düşük ve MMP-9 mRNA seviyeleri daha yüksekti.

Sonuç: Bu bulgular, PAD4, MPO, MMP-9 ve H3Cit'in, NET düzensizliğinin potansiyel biyobelirteçleri olduğunu ve özellikle kardiyovasküler bozukluklar olmak üzere COVID-19 sonrası semptomlara neden olabileceğini düşündürmektedir.

Anahtar Kelimeler: Kardiyovasküler Anormallikler, Sitrulline Histon H3, Nötrofil Hücre Dışı Tuzakları, Peptidilarginin Deiminazlar 4, Akut Post -COVID-19 Sendromu

INTRODUCTION

Coronavirus disease 2019 (COVID-19) arises from RNA virus, called the acute severe respiratory syndrome-coronavirus-2 virus (SARS-CoV-2) and properties a wide variety of medical complications (1). Concerning the data from the World Health Organization (WHO), globally, as of 30 November 2022, there have been more than 639 million confirmed cases of COVID-19 of whom at least 6 million have died (2). Clinical course and long-term effects are still not understood of the disease which ranges from asymptomatic to mild or severe patients, some requiring intensive care have serious complications and affect different organs and systems in the body (3). It was determined that 30% of asymptomatic and 80% of cases requiring hospital care may have post-COVID conditions when all cases were evaluated (4,5). Some of the systemic manifestations, and symptoms that develop after COVID are called "long-haul" "long COVID-19", "persistent COVID-19 symptoms", or "post-COVID- syndrome" and may continue for weeks, months, or even years. One of them is cardiac manifestation which includes, tachycardia, palpitations, dysrhythmias, chest pain, and tightness (6,7).

NETs involved in NETosis, a form of cell death dependent on neutrophils, are networks of DNA surrounded by histones and granular proteins. They capture and destroy invading pathogens in the extracellular space (8,9). Possible mechanisms of myocardial disorder in Covid 19; myocarditis caused by hyperinflammation and cytokine storm, cardiac myocyte damage caused by respiratory failure and hypoxia, development of hypercoagulation, and coronary microvascular thrombosis are endothelial damage in many organs including the heart (10). The most common cause of heart attack coronary artery thrombosis is associated with NET accumulating in the cardiac extracellular spaces resulting in both systolic and diastolic dysfunction (11).

Although there is not much data on Post-Covid-19, the symptoms that occur after the healing duration are not firsthand caused by the virus, but are related to the coagulopathies and inflammatory response of the body to heal during the disease duration. Uncontrolled NET formation in coagulopathies induced by Covid 19 reasons, acute cardiac injuries, thrombosis, sepsis, respiratory failure, and heart failure (12). It has been reported that NET dysregulation also may cause post-disease symptoms, and an imbalance occurs in genetic and epigenetic factors that neutralize pathogen invasion and manage NETosis (13).

Peptidylarginine deiminases 4 (PAD4) neutrophil histones by citrullinating, myeloperoxidase (MPO) neutrophil elastase by stimulating, provide chromatin condensation through histone modification during NET formation. Studies have found that citrullinated histone H3 (H3Cit) and the MPO-DNA complex are elevated in patients with COVID-19, and they are thought to be potential biomarkers for plasma NET formation (14,15). Because of their capacity to disrupt the extracellular matrix, regulate tissue structure, and induce proteolysis, matrix metalloproteinases (MMPs) cause atherogenesis and vascular damage. Studies have shown that the amount of matrix metalloproteinases-9 (MMP-9) released during NETosis plays a role in endothelial integrity (16). One of the covid-sequelae in myocardial disorders, to determine the role of NETs, we aimed to measure the levels of PAD4, MPO, MMP-9, and H3Cit, which are involved in the molecular mechanism of NET formation.

MATERIAL AND METHODS

Study Population: Our prospective case-control study consisted of individuals between the ages of 18 and 45 who applied to the Cardiology Clinic of Kahramanmaraş Sütçü İmam University (KSU) Faculty of Medicine. Forty patients with histories of or confirmed SARS-CoV-2 infection and cardiological complaints lasting at least two months were included, along with 40 healthy individuals without histories of COVID-19 and normal sinus rhythms on an electrocardiogram (ECG) (17). Those with a history of systemic disease (diabetes, hypertension, thyroid disorder, etc.), morbid obesity, heart valve disease, left ventricular hypertrophy, electrolyte imbalance, permanent pacemaker implantation, atrial fibrillation, branch block or other intraventricular conduction defects, smoking, alcohol use, or cardiac problems were excluded. Those using drugs that affected the heart's rhythm (antiarrhythmics, antihistamines, etc.) were not included in our study.

Enzyme-linked immunosorbent assay (ELISA): Peripheral blood was collected from controls and patients. Blood samples were stored at room temperature for 30 min to allow for clotting and were then centrifuged at 2,000 × g for 15 min at 4°C. Serum was collected, mixed by inverting, and aliquoted into 0.5 mL Eppendorf tubes and stored at −80°C until further processing time. A quantitative sandwich ELISA was performed to assess serum levels of PAD4, MPO, and H3Cit (ELK Biotechnology, ELK3904, ELK1062, ELK8743, Wuhan, China) following the manufacturer's instructions. The absorbency of the reaction product was measured at 450 nm using a micro-plate reader.

Real-Time PCR: Lymphocytes were isolated from heparinized whole blood using Ficoll-Paque Plus solution as directed by the manufacturer. Separated mononuclear cells and plasma were then collected and stored at −80◦ C until use for RNA isolation. Total RNA extraction was made using TRIzol reagent (Life Technologies) on ice as described by the suppliers. Thereafter, the integrity and purity of the total RNA were measured using by spectrophotometer and agarose

gel. cDNA was synthesized using the reverse transcription system (Applied Biosystems™ High-Capacity cDNA Reverse Transcription Kit). QPCR was performed to measure human PAD4, and MMP-9 using a commercially available Taqman gene expression assay kit (Applied Biosystems). Expression data were normalized using the housekeeping gene GAPDH for each sample and fold change values were calculated using the $2^{-\Delta\Delta Ct}$ method.

Statistics: In the evaluation of the data, the conformity of the variables to the normal distribution was examined using the Shapiro-Wilk test. Statistical analyses for the ELISA and qPCR experiments were performed using the two-tailed Mann -Whitney test and independent samples t-test (Prism 8, GraphPad Software Inc., San Diego, CA). A P-value of ≤ 0.05 was considered significant.

RESULTS

The study groups consisted of forty patients who have a history of COVID-19 infection, 3 months after the onset of the disease and cardiological complaints durable at least 2 months, and forty healthy individuals without a history of COVID-19.

Plasma levels of PAD4, which supports NET formation by inducing chromatin condensation via histone citration, were higher in the post-COVID-19 group compared to the without histories of COVID-19 group, but no statistically significant difference was observed ($p \geq 0.05$, $p = 0.38$) (Figure 1A). PAD4 mRNA levels were decreased in the post-COVID-19 group compared to the control group, and there was a significant difference between the groups in terms of PAD4 mRNA levels ($p \leq 0.05$, $p = 0.001$) (Figure 2A). MMP-9 mRNA levels were also found to be high in the post-COVID-19 cases, but the results were not statistically significant ($p \geq 0.05$, $p = 0.725$) (Figure 2B). Citrulline H3 and MPO levels, which are important plasma biomolecules for NET formation, were found to be above in the post-COVID-19 group than in the control group, and this difference was statistically significant ($p \leq 0.05$, $p = 0.003$, and $p = 0.0487$) (Figures 1B, 1C).

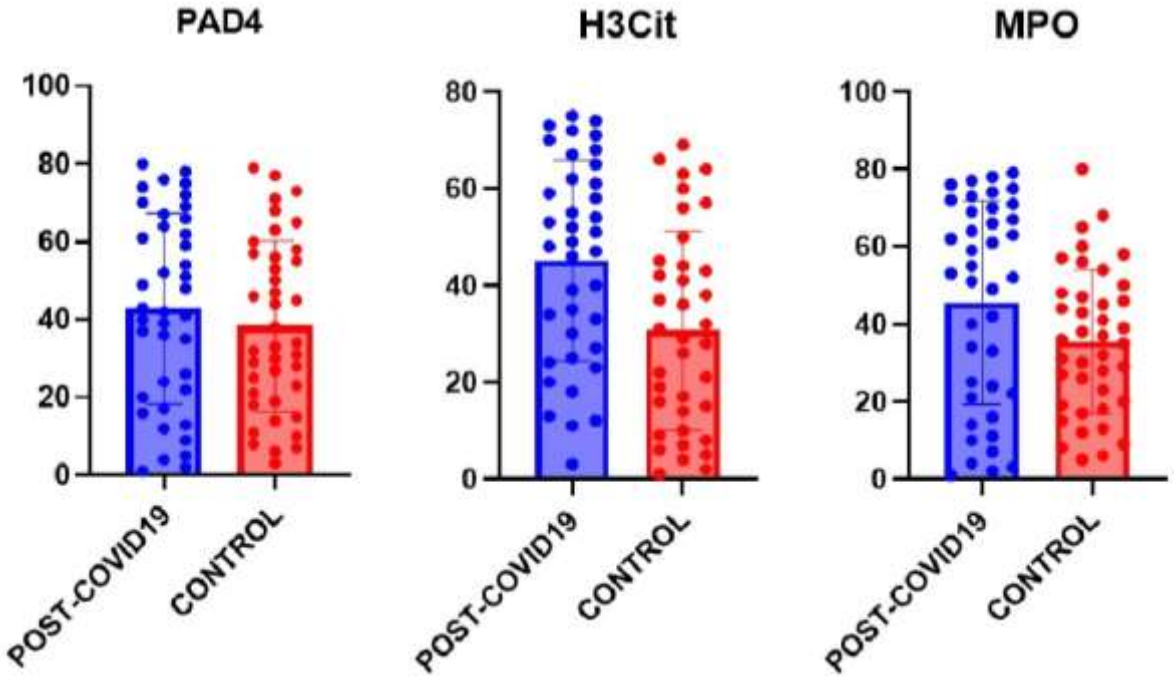

Figure 1. Plasma molecules responsible for NETs formation: **A)** PAD4 **B)** H3Cit, **C)** MPO were measured by Elisa in individuals per group. The plasma level of molecules was calculated and groups were compared by a non-parametrical test (Mann-Whitney Rank Sum Test) with GraphPad Prism software (version 8.0.2). Results were expressed as medians and interquartile ranges. * P-values were considered significant if ≤ 0.05.

DISCUSSION

To understand the pathologies mediated by NETs that develop after COVID-19, we aimed to indicate the levels of PAD4, MPO, MMP-9, and H3Cit biomolecules, which are involved in the molecular mechanism that governs disease-related NETosis, in the patient group with cardiological complaints for at least two months after COVID-19. Studies on COVID-19 sequelae and their molecular mechanisms are increasingly prevalent, but our study is the first in which these biomarkers were investigated together in this patient groupIn a study in which septic shock and critical COVID-19 cases were compared with a healthy control group in terms of NET formation, the H3, circular H3, neutrophil elastase, and MPO in the nucleosome content were analyzed. In that study, circulating nucleosome and neutrophil activation indicators were found to be above in the COVID-19 and septic shock groups (15).

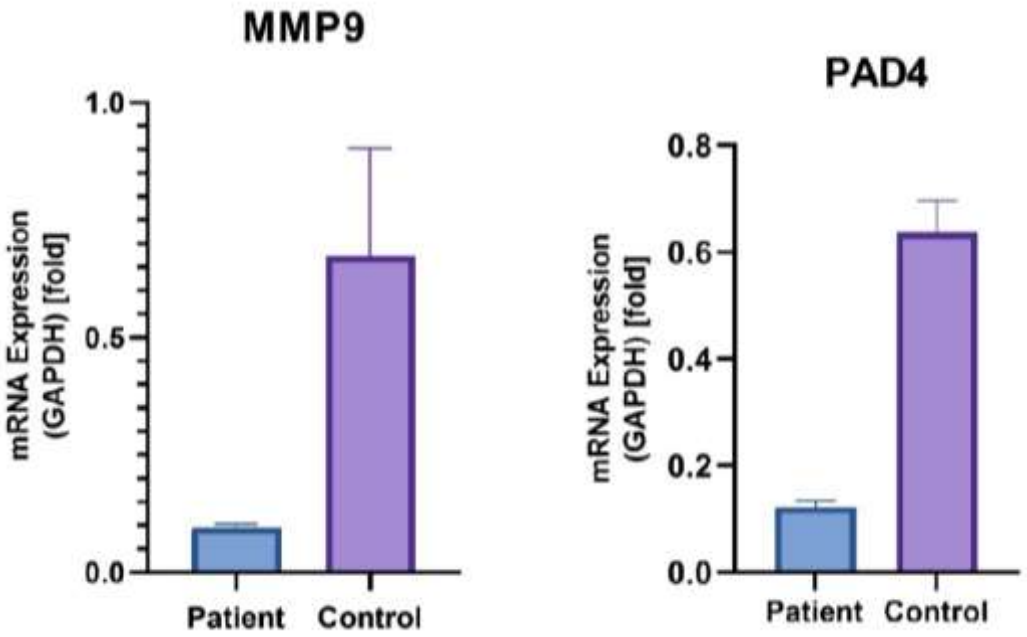

Figure 2. A) MMP-9 **B)** PAD4 were measured by real time RT-PCR in per group. The expression level was calculated as the mean ± s.d. for each group as individual data points using the relative expression (fold change over CONT) by the 2-ΔΔct method, where Ct is the threshold cycle. Groups were compared by a unpaired t test with GraphPad Prism software (version 8.0.2). Results were expressed as medians and interquartile ranges. * P-values were considered significant if ≤ 0.05.

In another study comparing hospitalized patients with a diagnosis of COVID-19 and a healthy group, the NET concentration was found to be higher in the COVID-19 group. In the same study, plasma MPO levels were found to be above in the COVID-19 group, confirming previous findings. Consistent with this research, in our study, plasma MPO levels were found to be higher in the post-COVID-19 group. At the same time, it has been determined that PAD4, which catalyzes arginine stratification and mediates NET release from neutrophils, creates a systemic increase in NETs (18). Consistent with this, in our study, PAD4 plasma levels were found to be above in the post-COVID-19 group. The increase in thromboembolic events and cardiovascular diseases following COVID-19 and its relationship to NETs and their production of long-term pathologies are still controversial (19). It has been determined that thrombotic complications occurring in COVID-19 are responsible for mortality and morbidity. Studies have shown that thrombosis in patients with COVID-19 affects both arterial and acute coronary syndrome, venous circulation, deep vein thrombosis, pulmonary embolism, and heart attack. It has been determined that NET residues, which are manifested by the presence of circular DNA, citrulline H3, and MPO-DNA complex, are abundant in the blood of patients with SARS-CoV-2, while neutrophil-platelet aggregates and neutrophil activation indicators increase in COVID-19 cases (20). In our study with patients with cardiological complaints after COVID-19, it was determined that plasma levels of PAD4, MPO, MMP-9, and H3Cit, which activate NETosis, increased. Histological studies have shown that NET increase causes vascular damage, and NET-related immuno-thrombosis is associated with organ damage in severe COVID-19 cases (21,22). NET-rich thrombi, platelets, and fibrins have been found in the lungs, hearts, and kidneys (20,23).

In a study conducted with 282 people with suspected coronary artery disease, coronary tomographic angiography and measurement of NET markers (citrulline H3, MPO-DNA complex) determined that these markers were also associated with the severity of coronary disease, prothrombotic state, and major side effects of cardiac disorders. In that study, it was reported that NET formation may contribute to the formation of atherosclerosis (24). Histological studies have demonstrated the presence of NETs in the lumen of mouse and human atherosclerotic lesions (25). In this study, in which we set out with the hypothesis that uncontrolled NET formation may lead to cardiovascular disorders after COVID-19, the biomarkers state involved in the molecular mechanism of NETosis are correlated with the results in the intersection of cardiovascular disorders, COVID-19, and NET. Our sample size for the study is limited, and we were unable to investigate other molecules involved in the same pathways as the biomarkers we examined. As the sample size was limited, the subjects in all groups could not be subdivided according to the test score. Therefore, further studies with a larger study population are needed to clarify this subject. In upcoming studies, the examination of more biomarkers is planned.

In COVID-19 patients, MMP-9 is increased, and this has been reported to stimulate platelet and neutrophil activation and NET formation in vitro (26). In another study, the neutrophil activation markers NET and MMP9 were associated with the severity of the disease in COVID-19 cases requiring intensive care (27). In this study, MMP9 mRNA levels were found to be higher in patients who had COVID-19 compared to the control group, which is consistent with the literature.

CONCLUSION

This study reveals that PAD4, MPO, MMP-9, and H3Cit appear to be potential biomarkers in NET dysregulation, which may cause certain post-COVID-19 symptoms – especially cardiovascular disorders.

Acknowledgments: This study was supported by the KSU Scientific Research Projects Coordination Unit under number 2021/2-33 M.

Ethical Approval: For this study, a certificate of ethical approval was obtained from the KSU Faculty of Medicine Non Interventional Clinical Research Ethics Committee with the meeting decision 11.01.2021/04 dated and numbered written informed consent was obtained from each patient before inclusion in the study.

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RESEARCH ARTICLE

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Evaluation of Nasal Mucociliary Clearance in Recently Diagnosed Covid-19 Patients Before Treatment

ABSTRACT

Objective: Our study aims to evaluate the nasal mucociliary clearance (NMC) in Covid-19 patients who have been recently diagnosed and not been treated yet and investigate how Covid-19 affects NMC.

Methods: A total of 120 participants, who applied to Düzce Atatürk State Hospital between September and November 2020, were included in our study. 60 of them were the participants, diagnosed with Covid-19. And 60 of them were the control group. The age range was 18 to 66. 60 participants, diagnosed with Covid-19 and not yet treated, were included in our study. Those with taste disorders were excluded from the study. The control group consisted of 60 healthy volunteers. NMC was evaluated using a saccharin test. The results were compared in the Statistical Package for Social Sciences (SPSS).

Results: The study group, which consisted of 60 Covid-19 participants of whom treatment was not yet started, and the 60-participant healthy control group were evaluated in our study. The average age of the study group was 40,72±12,96 and 39,16 in the control group. The average NMC was 15,95±3,37 in the study group, and 8,38±1,03 in the control group. When evaluated statistically, it was found higher in the study group ($p<0,001$).

Conclusions: NMC acts as a barrier for inhaled foreign bodies. It is a non-specific protection system against airborne pathogens. Consequently, NMC extends in Covid-19 patients.

Keywords: Covid- 19, Nasal Mucociliary Clearance, Smell Disorders.

Yeni Tanı Almış Kovid-19 Hastalarında Tedavi Öncesi Nazal Mukosiliyer Temizliğin Değerlendirilmesi

ÖZET

Amaç: Çalışmamızın amacı yeni tanı almış ve henüz tedavi başlanmamış COVİD 19 hastalarında nasal mucocilier klirensi (NMC) değerlendirerek covid 19 un NMC yi nasıl etkilediğini araştırmaktır.

Gereç ve Yöntem: Çalışmamıza Düzce Atatürk Devlet Hastanesine 2020 yılı eylül-kasım ayları arasında başvuran toplam 120 kişi alındı. Bunların 60 tanesi covid 19 tanısı almış hastalardı. 60 tanesi de kontrol grubuydu. Yaş aralığı 18-66 ydı. Çalışmamıza covid 19 tanısı almış ve tedavi başlanmamış 60 kişi alındı. Tat bozukluğu olanlar çalışmaya alınmadı. Kontrol grubu olarak ta 60 sağlıklı gönüllü alındı. NMC sakkarin test ile değerlendirildi. Sonuçlar Statistical Package for Social Sciences (SPSS) te karşılaştırıldı.

Bulgular: Çalışmamızda 60 Covid 19 tanısı alan ve tedavi başlanmamış çalışma grubu ve 60 sağlıklı kontrol grubu değerlendirildi. Yaş ortalaması çalışma grubunda 40,72±12,96 kontrol grubunda 39,16 idi Ortalama NMC çalışma grubunda 15,95±3,37idi, kontrol grubunda ise 8,38±1,03 idi. İstatiksel olarak değerlendirildiğinde çalışma grubunda daha yüksek bulundu ($p<0,001$).

Sonuç: Sonuç olarak NMC Covid 19+ hastalarında uzamaktadır.

Anahtar Kelimeler: Covid- 19, Nazal Mukosilyer Klirens, Koku Bozuklukları

INTRODUCTION

Covid-19 is a disease that was first seen in Wuhan city, capital of Hubei province of China, and turned into a pandemic by spreading around the world (1). On January 30, 2020, the World Health Organization (WHO) Emergency Committee declared Covid-19 a global health emergency depending upon the increasing number of cases in China and other countries (2). The main symptoms of Covid-19 are fever, cough, fatigue, mild dyspnea, sore throat, headache, conjunctivitis, and gastrointestinal problems (3). Covid-19 can be overcome with asymptomatic or mild findings as well as severe that can cause the death of patients. The final diagnosis is made by evaluating the nasal and throat swabs by PCR test. There has yet been no proven effective treatment method (3). For this reason, most countries impose quarantines and curfews to reduce the number of cases. Besides the main symptoms, patients may also experience different symptoms. One of them is smell and taste disorder. Some Covid-19 patients apply with smell and taste disorder complaints. Its pathophysiology has not been yet fully elucidated. The most important transmission source of the disease is through the respiratory tract.

NMC acts as a barrier for inhaled foreign bodies. It is a non-specific protection system against airborne pathogens. The captured particles and microorganisms are transported in the mucus film to the pharynx and eliminated by coughing or swallowing. Therefore, it has a very important role in the protection of the upper and lower respiratory tracts, and the removal of inhaled foreign bodies (4). Disruption of NMC results in the stasis of secretions and leads to secondary infections (5). Deaths due to Covid-19 occur as the disease induces pneumonia, ARDS (acute respiratory distress syndrome), and multi-organ failure (6-8).

In this study, we aimed to investigate NMC, which acts as a protective barrier for the upper and lower respiratory tracts.

MATERIAL AND METHODS

Study Design: Our study was carried out at Düzce Atatürk State Hospital between September and November 2020, after the Düzce University University (date 07.09.2020 and decision 2020/167) Ethics Committee approval was received. The written informed consent form was obtained from all the participants, participating in the study. In this study, under the 80% power and 5% Type I error conditions, the minimum sample size, required to determine the 1-unit difference between the healthy individuals and Covid-19 patients, was calculated as 52 individuals with an effect size of 0,558. Accordingly, it was planned to work with at least 104 individuals, 52 in each group. The power analysis was performed with the G*Power v.3.1.9.4 package program.

Study Population: Our study was conducted between September and November 2020. 60 participants, who applied to Düzce Atatürk State hospital, had a PCR test, and were diagnosed with definite Covid 19, were included as the study group. NMC test was implemented on the participants before the treatment. 60 healthy people, applying to our hospital without any symptoms, were included in the study as the control group, who are smokers, had nasal surgeries before, are diagnosed with allergic rhinitis and/or asthma, have systemic diseases were not included in the study. Covid-19 patients who are smokers, had nasal surgeries before, are diagnosed with allergic rhinitis and/or asthma, have systemic diseases were not included in the study. The examinations and mucociliary clearance tests of all patients were performed by the same researcher. Before testing, each participant, included in the study, underwent an endoscopic examination. 0 degree 4mm Wolf brand telescope was used as the endoscope.

Measurement of Nasal Mucociliary Clearance: The saccharin test was used to evaluate NMC. Saccharin test is a frequently preferred method for the evaluation of NMC as it is inexpensive, practical, and reliable. It was first identified in 1974 and modified by Rutland and Cule in 1980 (9,10). Everyone, included in the control and study group, was evaluated by the same researcher. Before the test was performed, the participants were informed about how it was conducted. The participants watched an instructive video, showing how the test was performed. They were warned not to wipe their noses during the test. 1 mg saccharin was placed in the medial part of the concha, 1 cm ahead of the inferior concha head. The patients were informed that they should be in a sitting position during the test. When the sweet taste in their mouths was present, it was measured with a stopwatch and recorded as NMC time.

Statistical Analysis: The distribution of the data was examined with the Kolmogorov-Smirnov test. The group comparisons for variables with normal distribution were made with the Independent samples t-test and for the ones, not showing normal distribution, they were made with the Mann-Whitney U test. Pearson's chi-square test was used in the analysis of categorical variables. Statistical analyzes were made with the SPSS v.22 package program, and the significance level was considered 0,05.

RESULTS

A total of 120 participant, 60 in the study and 60 in the control group, participated in our study. There were 28 men and 32 women in the study group. And there were 30 men and 30 women in the control group. The average age of the study group was 40,72±12,96 and that of the control group was 39,16±7,83 (Figure 1).

When we compared the average age of the groups, it was not statistically significant. While the average NMC was 15,95±3,37 in the study group, it was 8,38±1,03 in the control group (Figure 2).

The average NMC in the study group was found to be statistically higher than the control group (p<0,001) (Table 1).

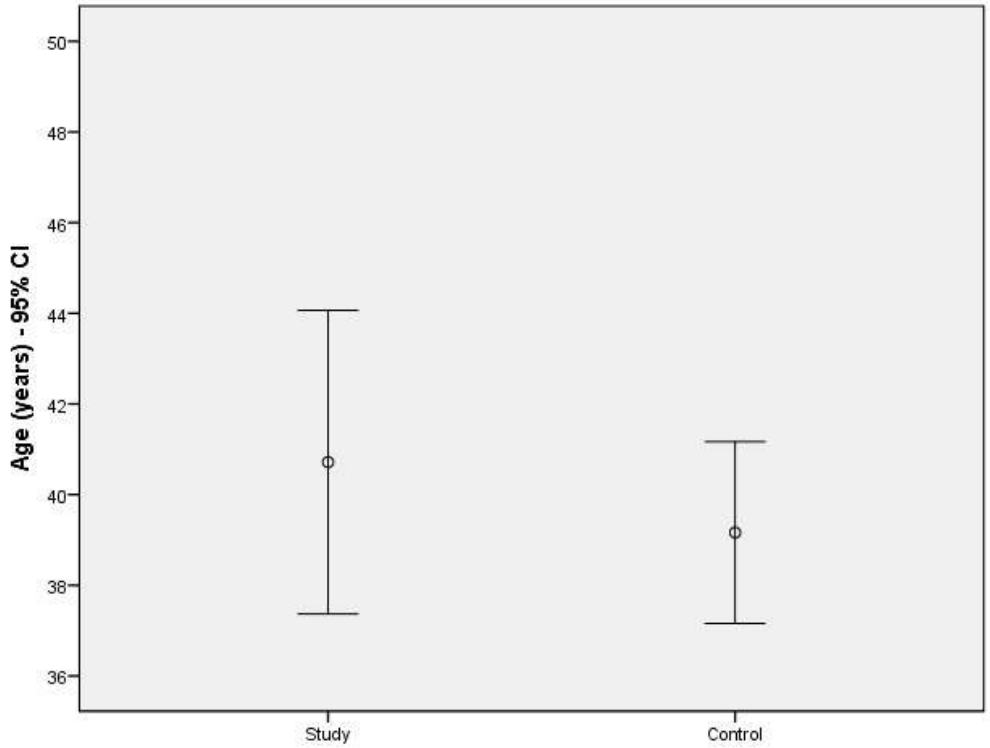

Figure 1. Age distribution of control and study groups

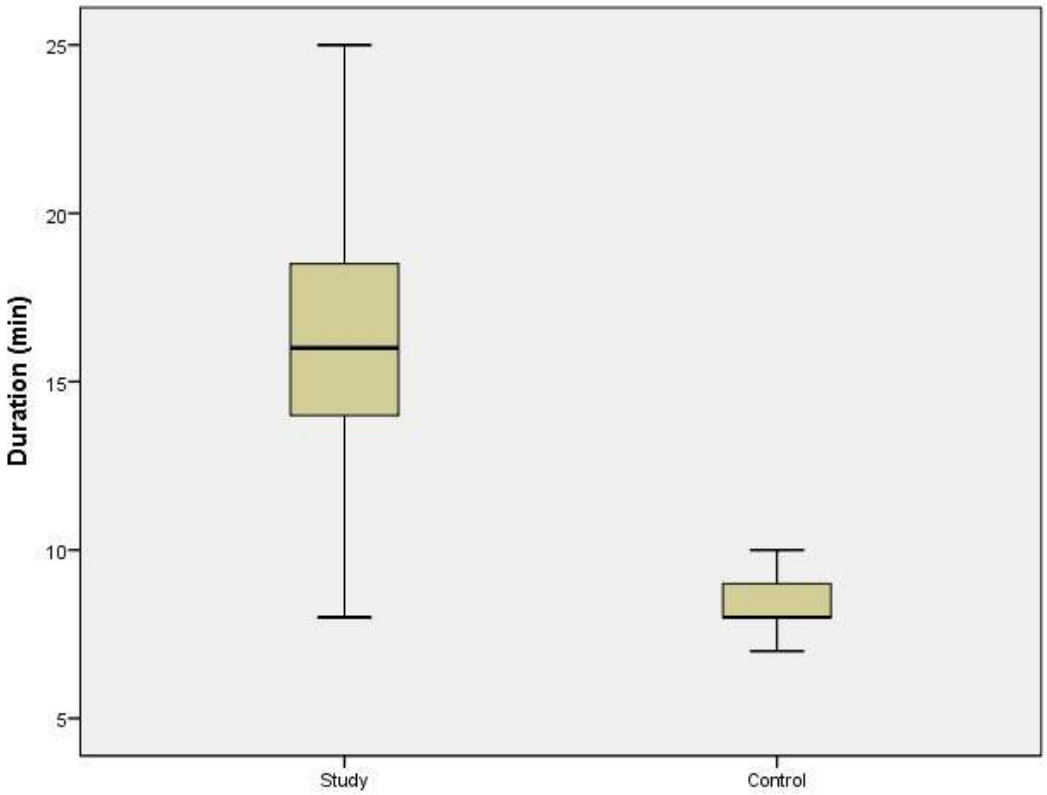

Figure 2. NMC time of study and control groups

Table 1. Mean age, mean NMC time and gender distribution of control and study groups

	Study (n=60)	Control (n=60)	p
Gender, n (%)			
Male	28 (46.7)	30 (50.0%)	0.648
Female	32 (53.3)	31 (50.0%)	
Age (years), mean±SD	40.72±12.96	39.16±7.83	0.428
Duration (min), mean±SD	15.95±3.37	8.38±1.03	**<0.001**
median (IQR) [min-max]	16 (5) [8-25]	8 (1) [6-10]	

SD: standard deviation, IQR: interquartile range

DISCUSSION

When the control and study groups were compared in our study, it was determined that NMC was statistically found higher in the study group. When the men and women in the study group were compared, there was no statistical difference. When the male and female individuals were separately compared between the study and control groups, there was a statistically significant difference. In the study of Koparal et al., NMC was found to be high in Covid-19 patients (11). Our study's difference from this study is NMC was performed immediately after the patients were diagnosed to reveal if Covid-19 objectively affects NMC. Another study by Ozturk et al. showed that the nasal defense mechanism was weakened in the early period after Covid 19 infection (12). Pezato et al. found in their study that NMC increased in dyspneic Covid 19 patients (13).

The nose forms the beginning of the respiratory tract. NMC in the nasal mucosa is a protective barrier of the respiratory tract. It is a non-nonspecific defense mechanism. It enables the removal of harmful substances by holding the particles in the nasally taken air. Normal NMC time in humans is considered to be 12-15 minutes (14). Disruption of NMC leads to stasis of secretions and infections. Many factors such as chronic rhinosinusitis, nasal polyps, septum deviation, allergic rhinitis, smoking, moisture, temperature affect NMC (15-17). There are different methods for evaluating NMC; however, we preferred the saccharin test in our study as it is cheap, easy to apply, and gives reliable results. This test is a practical and reliable test that has been widely used for many years (18).

Covid-19 is a viral air-borne disease that is transmitted by air. The incubation period is between 3 and 14 days (19). Patients apply to hospitals with nonspecific symptoms such as fever, cough, dyspnea myalgia, and/or diarrhea (20). The disease can be asymptomatic or fatal in some people. Especially in older people, it can result in severe pneumonia and death by leading to lower respiratory tract infection. NMC time extends with age (21). Petrov VV determined in his study that the nasal cavity mucous membrane underwent specific changes with age (22). This change in the nasal mucosa may be causing an increase in NMC. We found that NMC extended with age in our study as well. Another reason why these people suffer from severe pneumonia may be that the pathogens cannot be removed sufficiently due to the extension of NMC time with age. Anosmia is a distinct sign of covid 19 (23). Covid-19 may be affecting neural cells in the olfactory epithelium or the developed inflammation may be leading to anosmia and loss of taste by affecting the non-neuronal cells (24,25). Covid-19 patients can apply with a sudden loss of smell without any other symptoms (23,26). The disease's pathophysiology and how it affects the nose have not been fully elucidated. Goblet cells and ciliated epithelial cells in the nasal mucosa might be the first regions of Covid-19 (27). People with pathologies that cause NMC extension such as chronic rhinosinusitis, nasal polyp, septum deviation, may be undergoing a more severe disease. Extended NMC may ease the incubation of the virus in the nose. This can be a reason why some young people have a severe illness. Other studies are needed regarding this. For the first time in 2007, Suzuki et al. detected rhinovirus, coronavirus, parainfluenza virus, and Epstein-Barr virus in the nasal secretions of patients with post-viral smell disorder (28,29). We found out in our study that the NMC time statistically extended in covid 19 patients compared to the control group. There may be a relation between the NMC extension and that some patients undergo severe pneumonia and some get off lightly. Other studies which evaluate the relation between pneumonia severity and NMC time are needed.

The conducted studies showed that the first transmission place of Covid-19 is nose and throat. In addition, it was detected that the viral load was higher in the nasal cavity in both symptomatic and asymptomatic Covid-19 patients. Chinnapaiyan et al reported in their study that HIV (human immunodeficiency virus) infection disrupted tracheobronchial mucociliary clearance, and caused recurrent pneumonia and tracheobronchitis (30).

CONCLUSION

As a conclusion, our study shows that NMC has extended in Covid-19 patients compared to healthy individuals. We hope that our study will contribute to other studies in understanding the pathophysiology of the disease.

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RESEARCH ARTICLE

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Carbapenem-Resistant *Enterobacterales* Infections and Their Association with Rectal Colonization

ABSTRACT

Objective: Carbapenem-resistant *Enterobacterales* (CRE) infections have limited treatment options, and these infections are associated with high mortality rates. Asymptomatic carriers colonized with CRE contribute to the spread of CRE in hospitals. It was aimed to determine the frequency of CRE isolates detected in our center, carbapenemase ratios in these strains, carbapenemase genes, antibiotic resistance profiles, rectal CRE colonization rates and to evaluate various clinical features of CRE infections.

Methods: *Enterobacterales* species isolated from various specimens and *Enterobacterales* species isolated from rectal swab specimens sent for colonization screening were examined. Patients with CRE colonization in rectal swab samples were examined for the development of CRE infection at a later time. CRE isolates were examined for carbapenemase production and the presence of carbapenemase gene.

Results: 14521 *Enterobacterales* (10161 *E. coli* and 4195 *K. pneumoniae*, 165 *Citrobacter*) isolates were examined. Carbapenem resistance was detected in 8.9% of these strains. CRE was detected in 4.7% of 15695 rectal swab samples evaluated for colonization. In 23.4% of the patients with CRE colonization, CRE growth was detected in other samples besides the rectal swab in the later period. It was observed that CRE infections developed on average 21 days after colonization.

Conclusions: CRE infections have started to emerge as a factor not only in hospitalized patients but also in community-acquired infections. Our study also showed that CRE colonization could be a significant risk factor for the development of infection. Therefore, early screening detection to detect colonization can help prevent or limit CRE infections with appropriate isolation methods.

Keywords: Carbapenem-Resistant *Enterobacterales*, Colonizations, Carbapenemase.

Karbapenem Dirençli *Enterobacterales* Enfeksiyonları ve Rektal Kolonizasyon ile İlişkisi

ÖZET

Amaç: Karbapenem dirençli *Enterobacterales* (CRE) enfeksiyonlarının tedavi seçenekleri sınırlıdır ve bu enfeksiyonlar yüksek mortalite oranları ile ilişkilidir. CRE ile kolonize olan asemptomatik taşıyıcılar, CRE'nin hastanelerde yayılmasına katkıda bulunur. Bu çalışmada: merkezimizde saptanan CRE izolatlarının sıklığının, bu suşlardaki karbapenemaz oranlarının, karbapenemaz genlerinin, antibiyotik direnç profillerinin, rektal CRE kolonizasyon oranlarının belirlenmesi ve CRE enfeksiyonlarının çeşitli klinik özelliklerinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Çeşitli örneklerden izole edilen *Enterobacterales* türleri ve kolonizasyon taraması için gönderilen rektal sürüntü örneklerinden izole edilen *Enterobacterales* türleri incelenmiştir. Rektal sürüntü örneklerinde CRE kolonizasyonu olan hastalar daha sonra CRE enfeksiyonu gelişimi açısından incelendi. CRE izolatları karbapenemaz üretimi ve karbapenemaz geni varlığı açısından incelenmiştir.

Bulgular: 14521 *Enterobacterales* (10.161 *E. coli* ve 4195 *K. pneumoniae*, 165 *Citrobacter*) izolatı incelendi. Bu suşların %8.9'unda karbapenem direnci saptanmıştır. Kolonizasyon için değerlendirilen 15695 rektal sürüntü örneğinin %4,7'sinde CRE saptanmıştır. CRE kolonizasyonu olan hastaların %23,4'ünde ilerleyen dönemde rektal sürüntü dışında diğer örneklerde de CRE üremesi saptandı. CRE enfeksiyonlarının kolonizasyondan ortalama 21 gün sonra geliştiği gözlendi.

Sonuç: CRE enfeksiyonları sadece hastanede yatan hastalarda değil toplum kökenli enfeksiyonlarda da bir etken olarak karşımıza çıkmaya başlamıştır. Çalışmamız ayrıca CRE kolonizasyonunun enfeksiyon gelişimi için önemli bir risk faktörü olabileceğini göstermiştir. Bu nedenle, kolonizasyonu saptamak için erken tarama tespiti, uygun izolasyon yöntemleriyle CRE enfeksiyonlarını önlemeye veya sınırlamaya yardımcı olabilir.

Anahtar Kelimeler: Karbapenem Dirençli *Enterobacterales*, Kolonizasyon, Karbapenemaz

INTRODUCTION

Carbapenem-resistant *Enterobacterales* (CRE) first appeared in the 1980s and has spread worldwide (1). CRE infections have limited treatment options and these infections are associated with high mortality rates (2). Asymptomatic carriers colonized with CRE contribute to the spread of CRE in hospitals. The gastrointestinal tract is the most critical reservoir for hospitalized patients, resulting in cross-contamination and infections. Therefore, CRE colonization has been recognized as an important risk factor for subsequent infection (3). It has been reported that approximately 50% more CRE infections develop in patients colonized with CRE than in non-colonized patients.

In patients colonized or infected with CRE; it has been reported that health care costs increased, length of hospital stay increased, mortality rates increased, and treatment failures were more common (4). Therefore, identifying colonized patients/carriers of CRE and taking the necessary infection control measures are crucial to halt the spread of CRE (1).

Carbapenem resistance in *Enterobacterales* generally results from the production of β-lactamases such as KPC and New Delhi metallo β-lactamase (NDM), extended-spectrum β-lactamase (ESBL), AmpC lactamase (AmpC) and/or outer membrane protein loss. The genes that cause carbapenem resistance are usually found on plasmids. This resistance can be spread by clonal expansion or by horizontal transfer of genes to naive bacteria (2). Carbapenemase-producing strains spread more quickly than non-carbapenemase-producing strains. More intensive infection control measures are required against these strains. Therefore, it is appropriate to examine carbapenem-resistant strains for carbapenemases production (5). The Centers for Disease Control and Prevention (CDC) recommends that clinical laboratories actively screen isolates for carbapenemase production in carbapenem-resistant *Enterobacterales* strains (6).

However, tests to determine the underlying mechanism of carbapenem resistance are not routinely performed by most clinical microbiology laboratories today. It is known that the efficacy of new antibiotics developed and put into use against resistant strains varies according to carbapenemase production and carbapenemase species. This highlights the importance of detecting carbapenemase production and carbapenemase species in CRE (7).

In this study, it was aimed to determine the frequency of CRE isolates detected in our center in the last five years, carbapenemase ratios in these strains, carbapenemase genes, antibiotic resistance profiles, rectal CRE colonization rates in intensive care units, and to evaluate various clinical features of CRE infections.

MATERIAL AND METHODS

Carbapenem-resistant *Enterobacterales* species isolated from blood, tracheal aspirate, bronchoalveolar lavage (BAL), wound, urine, and sterile body fluid samples sent from intensive care and clinics between January 2017 and December 2021 were included in the study. CRE strains detected in the repetitive sample of the same patient were excluded from the study. However, strains that grew in different samples were included in the study.

In our hospital, patients hospitalized in intensive care units are routinely screened for CRE colonization from rectal swab samples on the first day of the week. In case of recurrent CRE growth in the rectal swab sample of the same patient, only the first growths were included in the study. The first CRE growth detected in the rectal swab sample of the patient was evaluated as colonization. It was examined whether there was growth in different samples of the patients who had growth in the rectal swab sample at a later time.

*Enterobacterale*s species were screened for carbapenem resistance. Eosin metilen blue (EMB) agar medium containing 2 mg/L ertapenem, which we prepared ourselves, was used for CRE screening. Antimicrobial susceptibility tests were performed with the VITEK 2® [Biomerieux, Marcy l'Etoile, France] automated system. Carbapenem resistance was confirmed by using the ertapenem gradient strip test [BioMérieux, Marcy l'Etoile, France] in strains found to have carbapenem resistance with VITEK 2®. To determine carbapenemase production, the Carbapenemaz inactivation test (CIM) was performed in accordance with the recommendations of Clinical & Laboratory Standards Institute (CLSI). Among the carbapenemase genes, blaIMP-1, blaKPC, blaNDM-1, blaOXA-48 and blaVIM genes were determined using the Gene-Xpert® System Carba R® kit [Cepheid, Sunnyvale, USA]. Ethics committee approval was not required because our study was conducted as a retrospective file review.

RESULTS

A total of 10,161 *E. coli* and 4195 *K. pneumoniae*, 165 *Citrobacter* growths were detected during the study period. It was observed that 1305 (8.9%) of these strains were carbapenem-resistant. When the distribution of CRE strains at the species level is examined, 250 (19.2%) were *E. coli*, 1046 (80.1%) were *K. pneumoniae*,11 (0.8%) were *Citrobacter spp.* was detected. When the distribution of CRE rates by years is evaluated; between 2017 and 2021, CRE rates were respectively; It was determined as 6.4%, 8.1%, 7.9%, 7.8%, and 14.1%. The distribution of CRE strains at the species level by years is shown in Table 1.

When the samples with CRE growth were examined; It was determined that 344 (26.3%) were

Table 1. Distribution of CRE isolates at the species level by years.

Year	*E. coli*	CR *E. coli*		*K.pneumoniae*	CR *K. pneumoniae*		*Citrobacter spp*	*CR Citrobacter spp*		Total CR	
	n	n	%	n	n	%	n	n	%	n	%
2017	2039	48	2.3	777	133	17.1	41	3	7.3	184	6.4
2018	1600	32	2	530	142	26.7	40	3	7.5	177	8.1
2019	2440	66	2.7	1020	208	20.3	31	2	6.4	276	7.9
2020	2012	61	3.0	837	164	19.5	25	2	8	227	7.8
2021	2070	43	2.0	1031	399	38.5	28	1	3.5	443	14.1
toplam	10161	250	2.4	4195	1046	24.9	165	11	6.6	1305	8.9

CR: carbapenem resistance

blood, 560 (42.9%) urine, 176 (13.4%) tracheal aspirate, and BAL, 225 (17.3%) other samples [wound, peritoneum, sterile, catheter].

A total of 1305 CRE strains were detected from 1225 patients. In 80 (6.5%) of the patients, CRE growth was observed in more than one sample.

Of the patients with CRE, 629 (51.4%) were treated in intensive care units, 461 (37.6%) were treated in wards, and 135 (11%) were admitted to polyclinics. Of the patients, 572 (46.7%) were male and 653 (53.3%) were female. The mean age of the patients was 65.7.

During the study period, 15695 rectal swab samples taken from hospitalized patients and sent to the laboratory for screening for CRE colonization were examined. CRE growth was detected in 745 (4.7%) of these rectal swab samples. All of the patients with CRE growth were hospitalized in the intensive care unit. Of the patients, 348 (46.8%) were female, and 397 (53.2%) were male. The mean age of the patients was 68.5. It was determined that these patients had CRE colonization. While 175 (23.4%) of these 745 patients who were evaluated as CRE colonization were hospitalized, CRE growth was detected in other samples other than rectal swab in the later period (in one or more samples).

In our study, 175 (13.4%) of 1305 CRE strains that we identified and evaluated as causative agents of CRE infection were infections that developed after rectal colonization. In patients with rectal colonization, CRE infections developing after colonization were observed to develop on average 21 days after colonization. Of the patients with colonization, 14 (8%) blood, 67 (38.2%) urine, 13 (7.4%) tracheal aspirate, 12 (6.8%) wound, 68 (39%) more than one CRE growth was detected in the sample.

Carbapenemase production was detected in 78% of the strains. The carbapenemase gene was investigated with Gene-Xpert® System Carba R® kit in 126 (91 positive, 35 negative) strains whose carbapenemase production was investigated by CIM. Carbapenemase gene was detected by Gene-Xpert® System Carba R® in 90 of the strains with carbapenemase production. When the distribution of carbapenemase genes detected from CRE isolates is examined; blaKPC was detected in 10 strains (11.1%), blaNDM-1 in 31 strains (34.4%), blaNDM+OXA-48 in 14 strains (15.5%), and blaOXA-48 in 35 strains (38.8%).

DISCUSSION

Despite all infection control measures, antibiotic resistance rates and infections caused by resistant bacteria are increasing all over the world (1,8,9). Resistance rates to meropenem and imipenem in *K. pneumoniae* strains in China; while it was 2.9% and 3.0% in 2005, in 2018; It has been reported to be 26.3% and 25% (10) It is seen that the rates of CRE vary between 1.1% and 60% worldwide (2,10-13). In our center, the rate of CRE was found to be 8.9% among all *Enterobacterales* species. While CRE infections were only encountered in hospitalized patients when they were first detected, community-acquired CRE infections have started to appear in recent years. Studies have reported that the prevalence of community-acquired CRE varies between 0% and 29.5% (14). 11.1% of CRE strains isolated in our study were isolated from the samples of patients admitted to outpatient clinics. The results of our study showed that CRE infections could be a risk factor not only for hospitalized patients but also for community-acquired infections.

The most common type of CRE isolated *K. pneumoniae*, followed by *E. coli* (2,15). It was determined that 250 (19.2%) of CRE strains detected in our center were *E. coli*, 1046 (80.1%) *K. pneumoniae*, 9 (0.7%) *Citrobacter spp.*

Carbapenem resistance seen in CRE strains can develop by different mechanisms. Among *Enterobacterales* species, the main mechanisms of carbapenem resistance are the production of carbapenemases such as KPC and NDM, ESBL, or AmpC beta-lactamase enzymes (16,17). Carbapenemase production in CRE strains ranges from 5% to 80% (16). This rate was found to be 78% in our center.

Carbapenemase resistance genes may vary depending on geographical differences (16-18). The most important mechanism of carbapenem resistance in *Enterobacterales* species is KPC-type

enzyme production. The KPC gene is usually transferred via plasmids. Therefore, there is a problem in controlling infections caused by KPC producing strains (16). In this study, blaKPC was found positive in 10 (11.1%) of the carbapenemase-secreting 91 CRE isolates in which carbapenemase gene regions were investigated by molecular method. NDM-1 poses a global health threat because it has high resistance rates and spreads rapidly and causes hospital epidemics (19). NDM rates have been reported to be between 3.3-54.5% in our country (15,20). NDM-1 was detected in 34.4% of CRE detected in our center, while NDM and OXA-48 were found to be associated in 15.5% of the strains. OXA-48-producing *Enterobacterales* species are spreading rapidly worldwide (21-23). Among the strains we examined in this study, the blaOXA-48 gene was found to have the highest rate (38.8%).

It is known that CRE infections usually develop before colonization (24). 1121 (86.4%) of 1305 CRE strains detected in our center were isolated as infectious agents. However, in 175 (23.4%) of the strains, rectal CRE colonization was detected first, and these strains were found to be infectious agents later on. Our study showed that rectal colonization with CRE is a significant risk factor for subsequent CRE infection.

Tischendorf et al. reported that infection developed in 16.5% of patients with colonization (24). McConvill et al. found that approximately 50% of patients colonized with CRE developed a CRE infection within 30 days and reported a 10.8-fold increase in infection rates compared to non-colonized patients. 9% of patients who developed rectal colonization developed CRE infection (4). After the worldwide spread of CRE, many centers have initiated infection control programs to limit the spread of CRE, the rate of infection, morbidity and mortality. Timely detection of carriers, separation of carriers from non-carriers, and activation of contact measures are important. In line with this information, our weekly routine screenings had continued since 2015, when the first CRE case was detected in our center, and rectal swab samples are taken from the patients hospitalized in intensive care units on the first day of the week and evaluated in the laboratories. We detected VRE colonization in our hospital at 4.7%. In 23.4% of the patients with CRE colonization, we encountered CRE strains as a factor in the later period.

The most important limitation of our study was that we could not search for carbapenemase detection methods and carbapenemase genes in all CRE strains.

In conclusion, CRE infections have started to emerge as a factor not only in hospitalized patients but also in community-acquired infections. Necessary measures should be taken in this regard as soon as possible. Our study also showed that CRE colonization could be a major risk factor for the development of infection. Therefore, early screening detection to detect colonization can help prevent or limit CRE infections with appropriate isolation methods. Detection of resistance mechanisms of CRE isolates will ensure that treatment measures are taken more accurately, and necessary measures will be taken to prevent the spread of pathogens.

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RESEARCH ARTICLE

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Educational Value of Youtube Videos in Dialysis Catheter Application

ABSTRACT

Objective: Youtube is one of the most popular video-sharing websites and can be a powerful tool for disseminating health information. The number and use of Youtube videos in the medical field is increasing, so there is a need to research its educational value. We examined dialysis catheter application videos' characteristics, usefulness, and scientific accuracy.

Methods: We performed a Youtube search with the keywords of "dialysis catheter" without selecting any filter in the English language in April 2022. The content of the videos, video sources, type of catheter mentioned in the video, presence of animation, and the accuracy of the information was evaluated. mDISCERN score was also determined to clarify the power of the accuracy.

Results: The evaluation showed that the number of videos with accurate information was 171 (83.4%) with a significantly higher mDISCERN score (2.85±0.59). Among the targeted videos, the mDISCERN score of the videos uploaded by healthcare professionals and the official institution was significantly higher. The average usefulness score was 1.96±0.23, and there was no significant difference between the sources.

Conclusions: It would be more appropriate to present the videos selected in terms of education and reliability under a sub-title such as "YouTube Medical Education" for use by medical professionals.

Keywords: Hemodialysis, Catheter, Youtube, Internet, Social Media.

Diyaliz Kateter Uygulamasında Youtube Videolarının Eğitimsel Değeri

ÖZET

Amaç: Youtube, en popüler video paylaşım sitelerinden biridir ve sağlık bilgilerini yaymak için güçlü bir araç olabilir. Medikal alanda Youtube videolarının sayısı ve kullanımı giderek artmakta olup bu nedenle eğitici değerini araştırma ihtiyacı doğmuştur. Diyaliz kateter uygulama videolarının özelliklerini, kullanışlılığını ve bilimsel doğruluğunu inceledik.

Gereç ve Yöntem: Nisan 2022'de İngilizce dilinde herhangi bir filtre seçmeden "diyaliz kateteri" anahtar kelimeleri ile Youtube araması yaptık. Videoların içeriği, video kaynakları, videoda bahsedilen kateter tipi, animasyon varlığı ve bilgilerin doğruluğu değerlendirildi. Doğruluğun gücünü netleştirmek için mDISCERN skoru da belirlendi.

Bulgular: Değerlendirme, doğru bilgi içeren video sayısının 171 (%83,4) olduğunu ve mDISCERN puanının (2,85±0,59) anlamlı derecede yüksek olduğunu gösterdi. Hedeflenen videolar arasında sağlık çalışanları ve resmi kurum tarafından yüklenen videoların mDISCERN puanı anlamlı olarak daha yüksek çıktı. Ortalama kullanışlılık puanı 1,96±0,23 idi ve kaynaklar arasında anlamlı bir fark yoktu.

Sonuç: Eğitim ve güvenilirlik açısından seçilen videoların "YouTube Tıp Eğitimi" gibi bir alt başlık altında tıp profesyonellerinin kullanımına sunulması daha uygun olacaktır.

Anahtar Kelimeler: Hemodiyaliz, Kateter, Youtube, İnternet, Sosyal Medya

INTRODUCTION

Being an indispensable element for hemodialysis (HD), the history of vascular access is rich (1). According to the United States Renal Data System, in 2021, it is reported that 80% of the patients started hemodialysis with a catheter, and 21% of these patients continued hemodialysis with a catheter in the first year (2).

Complications may appear in the existence of a catheter. Especially catheter-associated blood infections are an important reason for hospitalization, morbidity, and death. Therefore, the Centers for Disease Control and Prevention underline the importance of catheter care and aseptic conditions (3).

Likewise, catheter-associated complications are common in the early period of peritoneal dialysis and cause technical inadequacy (4). During catheter insertion, complications such as bleeding and bowel perforation may occur (5). Many studies conducted worldwide have shown that with the increase in the experience of doctors in inserting catheters, infectious complications decrease, and they become more effective in establishing a peritoneal access route (6).

Video broadcasting sites are frequently used today to obtain information. Especially on YouTube, more than 2 billion media are viewed per day. Recent surveys report that 8 out of 10 internet users access health-related information over the internet. As it is known, people with chronic diseases are increasingly using the resources on the internet to manage their conditions (7).

The number and use of Youtube videos in the medical field is increasing. Although this seems like a great opportunity, information with or without educational value can cause information pollution and chaos. Therefore, there was a need to explore the educational value of these videos. This study is the first to inspect Youtube as a source of data about dialysis catheters. This study aims to investigate videos about dialysis catheters on YouTube systematically.

MATERIAL AND METHODS

Video Selection and Search: In April 2022, 'dialysis catheter' was typed in English in the search bar of YouTube, a video broadcasting website, without selecting any filters. Three hundred seventy-five videos found after the search were evaluated. Videos with less than one minute in duration, irrelevant content, replications and commercials, and non-English and silent videos were excluded. While 170 videos were excluded, 205 videos were included in the study. The included videos were examined in the sense of the year they were published, the duration, the number of views, and the number of likes, dislikes, and comments. The content, video sources, type of catheter mentioned in the video, presence of animation, and the accuracy of the information they contain were evaluated. Catheters were divided into two main groups hemodialysis and peritoneal dialysis catheters. Hemodialysis catheters were also assessed into two groups temporary and tunneled. Video contents were grouped as catheter insertion, removal, care, complications, theoretical knowledge about the catheter, patient experience, and catheter insertion during the dialysis procedure. The accuracy of the video content was evaluated by a nephrologist and a cardiovascular surgeon as accurate and not.

The DISCERN questionnaire is valid and reliable for analyzing written consumer health information. It is the first standardized quality index of consumer health information that can be used by healthcare professionals and patients, and the general population as a critical assessment tool to assess health information. The mDISCERN score is a five-question scale adapted from a 16-question DISCERN vehicle developed by Singh (8) and Charnock et al. (9). Each criterion is rated as 1–0 (yes/no) and scored between 0 and 5. The scoring system was integrated into the study to avoid the subjective evaluation of the content regarding accuracy.

Global quality score (GQS) is a scoring system that has a five-point scale based on the quality of information and was created to evaluate its usefulness to patients. We used GQS to clarify the usefulness of the videos included in the study and compared the scores between the sources. Scores lower than three were accepted as very limited use to patients (Table 1).

Statistical Analysis: IBM SPSS Statistics 22 (IBM SPSS, Turkey) software was used for statistical analysis to evaluate the findings obtained in the study. Descriptive statistics were used to assess the data. Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as frequency and percentage. In determining the conformity of the data to the normal distribution, the Shapiro–Wilk test was used. Pearson v2 or Fisher' Exact test was used to comparing categorical variables. Continuous variables, on the other hand, were compared using Student's t-test or Mann-Whitney U test.

RESULTS

In total, 375 videos were watched. 170 (45.3%) of these videos were excluded from the study. Most of the excluded videos (n=47, 27.6%) were irrelevant to the content. Exclusion criteria are shown in Table 2, and the characteristics of 205 (54.7%) videos included in the study are shown in Table 3.

Table 1. Global Quality Score, mDISCERN Score Parameters

Global Quality Score
1. Low quality, video information flow weak, most information missing, not beneficial for patients
2. Usually, low quality and low flow of information, some listed information and many important issues are missing, very limited use for patients
3. Moderate quality, the insufficient flow of information, and some important information is sufficiently discussed, but some are poorly discussed and somewhat useful for patients
4. Good quality and generally good information flow. Most of the relevant information is listed, but some topics are not covered, useful for patients
5. Excellent quality and information flow, very useful for patients
mDISCERN Score
1. Are the aims clear and achieved?
2. Are reliable sources of information used?
3. Is the information presented balanced and unbiased?
4. Are additional sources of information listed for patient reference?
5. Are areas of uncertainty mentioned?

Table 2. Excluded videos and the reasons from the study

	n (%)
Dublicate videos	17 (10.0)
Non-English	27 (15.8)
Advertisement	45 (26.4)
Short recorded videos (less than 1 min)	29 (17.1)
Irrelevant	47 (27.6)
No voice included	5 (2.9)
Total	170 (100.0)

Table 3. Characteristics of the videos included in the analysis.

	n	%
Date (year) uploaded		
• 2012 and earlier	11	5.3
• 2013-2016	72	35.1
• 2017-2020	111	54.1
• 2021 (first 11 months)	11	5.3
Source of uploaded item		
• Doctor	92	44.8
• Nurse	23	11.2
• Medical website	28	13.6
• Patient experience	29	14.1
• Supply institution	14	6.8
• Television show	1	0.4
• Regular internet user	3	1.4
• Governmental/official institution (Hospital)	15	7.3
Video content		
• Instructional video for catheter insertion	105	51.2
• Instructional video for catheter care	16	7.8
• Theorotical information for HD catheters	35	17.1
• Complications of the catheter procedure	13	6.3
• Instructional video for catheter removal	4	1.9
• Patient experience	27	13.1
• Starting HD with the catheter	5	2.4
Types of HD catheters		
• Temporary HD catheter	93	45.3
• Permanent HD catheter	53	25.8
• Peritoneal HD catheter	59	28.7
Information accuracy		
• True	171	83.4
• False	4	1.9
• Experience/Uncertain	30	14.6
Was animation used in the content?		
• Yes	15	7.3
Total	205	100.0

HD, hemodialysis.

The average duration of 205 videos met the inclusion criteria was 6.1 ± 2.82 minutes (min: 1.52, max: 18.22). The number of likes of the videos was 154.284, and the video with the most likes received 18.212. The average number of likes was 6122.41 ± 4251. The total number of dislikes of the videos was 21.432, and the video with the most dislikes received 1624. The average number of dislikes was 252.14 ± 91.8. The total number of comments was 21.542, and the video with the most comments received 512. The average number of comments was 156.22 ± 101.24.

It was determined that 111 (54.1%) of the videos included in the study were released between 2017 and 2022. 76.9% (n=158) of the videos were uploaded by doctors, nurses, and medical websites or official institutions. Most videos included catheter insertion (n=105, 51.2%) and theoretical information about HD catheters (n=35, 17.1%). All videos (n=13, 6.3%) about complications that may occur during catheter insertion were edited by a doctor or a health facility. A nephrologist and a cardiovascular surgeon evaluated the accuracy of these video contents uploaded from different sources. The evaluation showed that the number of videos with accurate information was 171. (83.4%).

Videos about dialysis catheters were compared for information accuracy. When mDISCERN scores were compared between video sources, the scores of healthcare professionals and the governmental/official institution (Hospital) were significantly higher. These findings are given in Table 4. Video content uploaded by healthcare professionals (doctors, nurses), official institutions (Hospitals), and medical websites had significantly more accurate information content. No significant difference was observed between the correct and incorrect information content of videos uploaded from other sources. Among the related videos, the average GQS was 1.96±0.23, with no significant difference between the sources. The associated videos were accepted as "not useful" to patients due to an average score lower than three, even though the accuracy of video content uploaded by healthcare professionals (doctor, nurse) and official institutions (Hospital) were significantly higher.

Table 4. Comparison of the accuracy with respect to source of upload.

	True (n, %)	mDISCERN Score	Not true (n, %)	mDISCERN Score	*p value
Healthcare Professional (Doctor, nurse)	112	3.27±0.48	3	1.17±0.31	0.001*
Governmental/official institution (Hospital)	13	3.33±0.39	2	1.11±0.23	0.002*
Medical website	23	2.12±0.64	5	1.98±0.62	0.018
Others	23	2.27±0.61	24	1.91±0.29	0.061
Total	171	2.85±0.59	34	1.38±0.30	0.012

*P-value <0.05 accepted as the significant in comparison

DISCUSSION

Today, most people have access to information about their diseases both in written and visual form on the internet before going to the hospital. Although this information has sometimes increased the awareness of patients, inaccurate information can cause serious disinformation for the patient.

Similarly, there are many resources available for health education today. In this regard, internet video broadcasting sites are also frequently used, and Youtube stands out among them (10).

Although the number of these videos as sources is increasing daily, as we mentioned earlier, it is confusing how accurate the content of most videos is. Access to the video that provides precise information about the patient's disease and treatment is only possible by scanning the suitable materials, diagnosing the disease, and following the correct treatment procedures. This is almost impossible for the patient, and these situations need to be assisted and directed by healthcare professionals.

Moreover, most of the current health education and information videos are not prepared by health professionals and are advertisements. The procedures performed do not contain sufficient and accurate information about the diseases. There are many studies examining how helpful these videos are. Among these are studied by Ching et al. and similarly Gunes et al. on varicose veins. It has been stated in these studies that the uploader of most of the videos related to the varicose vein on Youtube is hospitals and official institutions (11, 12). Similarly, it was found in our study that approximately 76.9% of the videos were uploaded by official institutions or health professionals (doctors, nurses, and medical websites). Therefore, we believe that the high accuracy of the information in these viewed videos is associated with whether or not they are uploaded by professionals (information accuracy is 83.4%).

On the other hand, the fact that the videos are uploaded by health professionals or experts and the information is correct does not mean that it can be easily understood and beneficial to the patient. Medical language is used heavily in most video content, including surgical procedures. It can be used for the education of health professionals, but it may not be suitable for in-patient education. The article by Kyong No Lee et al. stated that surgical and academic videos would not be ideal for patients (13). To measure the usefulness of the content for patients, we used GQS, a tool to assess the site's overall quality, including information flow, ease of

use, and usefulness to patients. Even though mDISCERN scores of the videos uploaded by health-care professionals and governmental/official institutions were significantly higher, the GQS of videos from the health-care professionals and governmental/official institutions were similar, lower than three, and there was no significant difference between the groups. As a result, although the accuracy of the related content uploaded by professions or institutions was high, we can report that most of the videos in our study may not be suitable and valuable for patients as they include academic and surgical procedures.

Catheters are essential instruments of both hemodialysis and peritoneal dialysis treatments (14,15). Increasing knowledge and experience about catheter insertion can reduce catheter-related complications (14). YouTube can be an innovative tool for learning surgical procedures (16). Many of the videos included in our study (76.9% in total) were educational content videos prepared by healthcare professionals or healthcare facilities, were educational, and had high accuracy, proven by mDISCERN scores. This may be important for health professionals to increase visual memory.

The 205 videos included in the study were high-accuracy videos. However, their number of views was not high. On the other hand, the number of views of the media uploaded by others, which constitutes 23.1% of the videos, was 284.144 more, and this value was statistically significant (p=0.0021). Even though the number of videos with high accuracy is much higher, this restricts access without being filtered correctly and prevents the patient from accessing correct information. Like us, Gunes et al. observed in their study that the videos uploaded by health centers about varicose veins do not have a high viewing rate and usefulness. On the contrary, Yaylacı et al. searched for training videos on cardiopulmonary resuscitation on Youtube and emphasized that the videos uploaded by health centers are essential in community education (17). In light of this information, we think that uploading the videos about dialysis catheters in a language that can be understood by the audience, after being re-evaluated in the light of most healthcare professionals and healthcare facilities, will increase the quality of education and access to correct information primarily for the patients.

LIMITATIONS

The number and content of videos uploaded to the Internet are continuously variable. This study was created based on the videos that emerged from searching by typing the keyword of dialysis catheter on Youtube. Searches with other words and excluding videos with languages other than English reduced the number of videos evaluated.

CONCLUSIONS

Even though they were increasing uncontrollably and uploaded without any pre-evaluation, the video content on Youtube remains essential for health and patient education. Although the videos uploaded to Youtube about dialysis catheters have high information quality, they may not be able to communicate the correct information to the patient through the right communication channel because their language and content are primarily academic. Therefore, we believe that although these videos are essential for the experts in the selection, maintenance, and follow-up of the proper dialysis catheter, it is still necessary for the doctor to provide appropriate and accurate patient information. We also believe that there is a need for more professional and pre-evaluated videos in which the language and visuals are adjusted according to the target audience for accurate patient information on this subject. YouTube may be a "Procedures Consult"-like platform designed to help medical professionals prepare, perform, and test their knowledge of medical procedures (18). However, it would be more appropriate to present the videos eliminated in terms of education and reliability under a sub-title such as "YouTube Medical Education.". While YouTube-like platforms are known to have content moderation mechanisms, a sub-committee consisting of health professionals and academics, and soon even artificial intelligence technologies, could be utilized for the "moderation of medical training videos".

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RESEARCH ARTICLE

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Adherence Levels of Hypertensive Elderly Individuals and Associated Factors: A Cross-Sectional Study

ABSTRACT

Objective: Patient adherence, particularly in the management of chronic diseases, is an often overlooked but crucial aspect that is more important than medication treatment itself. It is also one of the major problems contributing to treatment failures. Our study aims to evaluate the adherence levels of elderly hypertensive individuals residing in the city center of Edirne, as well as the factors influencing adherence levels.

Methods: The study sample consists of 421 elderly hypertensive individuals registered with 52 primary healthcare units in the city center of Edirne. Data were collected using a questionnaire comprising 75 questions. The questionnaire included socio-demographic characteristics, factors that may affect patient adherence, and the Adaptation to Chronic Illness Scale consisting of 25 questions.

Results: Of the participants, 226 (53.7%) were female and 195 (46.3%) were male. The participants had an average adaptation score of 87.04±9.77, with a minimum score of 62 and a maximum score of 116. Younger elderly individuals had higher adaptation scores. Adaptation scores were lower for widowed individuals, illiterate individuals, and those living alone. Participants who were informed about their illness and treatment, involved their families, and had family support had higher adaptation scores.

Conclusions: The adherence levels of the elderly participants in our study were found to be below the expected level. Existing studies in the literature predominantly focus on medication adherence. Conducting studies that specifically target disease adaptation would enable a better understanding of patients and the development of new strategies to improve adherence levels.

Keywords: Patient Adherence, Hypertension, Elderly, Primary care.

Hipertansif Yaşlı Bireylerin Uyum Düzeyleri ve İlişkili Faktörler: Kesitsel Bir Çalışma

ÖZET

Amaç: Hasta uyumu, özellikle kronik hastalık yönetiminde göz ardı edilen, ancak ilaç tedavisinden çok daha önemli olan bir konudur. Tedavinin başarısız olmasının da en büyük sorunlarından biridir. Çalışmamızda Edirne il merkezinde yaşayan hipertansif yaşlıların hastalığa uyum düzeyleri ve uyum düzeyini etkileyen faktörlerin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışmanın örneklemini Edirne il merkezindeki 52 aile hekimliği birimine kayıtlı, 421 yaşlı hipertansif birey oluşturmaktadır. Veriler 75 sorudan oluşan bir anketle toplanmıştır. Anket içerisinde sosyodemografik özellikler, hasta uyumunu etkileyebilecek faktörler ve 25 sorudan oluşan Kronik Hastalıklara Uyum Ölçeği bulunmaktadır.

Bulgular: Katılımcıların 226'sı (% 53,7) kadın, 195'i (% 46,3) erkektir. Katılımcıların ölçekten aldıkları ortalama puan 87,04±9,77 olup minimum puan 62, maksimum puan 116'dır. Genç-yaşlıların uyum puanı daha yüksektir. Dul bireylerin, okuryazar olmayan bireylerin ve yalnız yaşayanların uyum puanı daha düşüktür. Hastalığı ve tedavisi ile ilgili, ailesi de bilgilendirilen, aile desteği olan katılımcıların uyum puanı daha yüksektir.

Sonuç: Çalışmamızda yaşlıların hastalığa uyum düzeyleri beklenen seviyenin altında bulunmuştur. Literatürdeki çalışmalar çoğunlukla ilaç uyumuna odaklanmaktadır. Hastalık uyumuna odaklanan çalışmalar ile hastayı daha iyi anlamak ve uyumlarını arttırabilmek için yeni stratejiler belirlemek mümkün olacaktır.

Anahtar Kelimeler: Hasta Uyumu, Hipertansiyon, Yaşlı, Birinci Basamak.

INTRODUCTION

The worldwide increase in life expectancy and decline in mortality rates have resulted in a significant rise in the elderly population (1). It is estimated that by 2050, the population aged 65 and over will nearly triple. Considering these universal demographic trends, issues related to the elderly become increasingly important in all societies (2). Hypertension, one of the most common chronic diseases, stands out among the elderly population due to its high mortality and morbidity rates.

Hypertension is a prevalent health problem worldwide, not only elderly, leading to significant complications (3). In 2015, the prevalence of hypertension in adults was around 30-45%, estimating that 1.12 billion individuals globally and over 150 million people in Central and Eastern Europe were hypertensive. It is projected that the number of hypertensive individuals will increase by 15-20% by 2025, reaching close to 1.5 billion (4). In Turkey, according to the PatenT2 (Prevalence, awareness and treatment of hypertension in Turkey 2) study conducted in 2012, the prevalence of hypertension was found to be 30.3%, and it was reported that the prevalence increases with advancing age (5). Despite the availability of various effective antihypertensive treatments, a significant number of patients worldwide still have inadequately controlled blood pressure. A recent multicenter study revealed that only 60% of treated hypertensive patients had their blood pressure under control (6). Various factors, including poor patient adherence to treatment, prescription errors, overly complex guidelines, and unsupportive healthcare systems, can explain the failure in hypertension management (4,7). Poor adherence poses a significant challenge since hypertension is mostly asymptomatic (8).

Adherence is defined by the World Health Organization as "the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a healthcare provider" (9). Adherence is recognized as a multidimensional phenomenon influenced by complex interactions among socioeconomic status, healthcare system, medical condition, treatment, and patient-related factors (8, 10). Patient-related factors affecting the adherence can include forgetfulness, the asymptomatic nature of the disease, and the presence of comorbid conditions. The initiatives aimed at improving patient adherence have shown that better weight control and blood pressure management have been achieved, reducing the economic burden and resulting in a 53.2% decrease in hypertension-related deaths and 57.3% decrease in all-cause life mortality rate. In another study where an educational program was implemented for hypertensive patients, a 39.7% improvement in blood pressure control and significant reductions in cardiovascular disease-related mortality rates were observed over a 5-year period, despite advancing age (9).

Clinicians' communication skills, the complexity of treatment regimens, polypharmacy, accessibility to healthcare, healthcare costs, and factors associated with the healthcare system and treatment also contribute to adherence. Identifying factors leading to inadaptability in patients and developing interventions to improve adherence can be facilitated by physicians (8). Accordingly, our study aims to assess the level of adherence to hypertension management among the elderly hypertensive population aged 65 and above residing in the city center of Edirne and provide recommendations to enhance their adherence.

MATERIAL AND METHODS

Our cross-sectional study includes a population of 19,731 individuals aged 65 and above registered at 52 family health centers in the city center of Edirne. To calculate the minimum sample size for the study, it was determined that 319 individuals needed to be included to achieve statistical significance with a prevalence of 30.3%, a 5% margin of error, and a 95% confidence level among the population of individuals aged 65 years and above. The population was categorized into three groups according to age: 65-74 (young-old), 75-84 (old), and 85 years and above (oldest-old) (11). Stratification was performed based on gender and age groups, ensuring that each family health center had at least one individual from each gender and age group. A total of 421 individuals were selected by random sampling between December 1, 2019, and March 15, 2020.

The research was conducted with the approval of the Trakya University Faculty of Medicine Scientific Research Ethics Committee (no:2019/349) and the Edirne Directorate of Public Health Primary Care Research Commission (no: 2019/10). Verbal consent was obtained from the participants, and the surveys were administered through face-to-face interviews.

The inclusion criteria for participation in the study were being registered at the family health centers in the city center of Edirne, being aged 65 and above, and having a diagnosis of hypertension. The criteria for exclusion from the study were having communication barriers.

The data was collected using a questionnaire created by the researchers through a literature review. The questionnaire consisted of 50 questions, which assessed the participants' sociodemographic and medical characteristics, their family's knowledge about hypertension, and the presence of family support. A 25-item Adaptation to Chronic Illness Scale (ACIS) was included to assess individuals' adherence to chronic diseases. The participant's blood pressure measurements were taken by the same researcher using a clinically validated digital

arm cuff blood pressure monitor (Omron M6 Comfort ®).

Adaptation to Chronic Illness Scale (ACIS): The Adaptation to Chronic Illness Scale was developed by Atık and Karatepe (12) in 2015. It is a 5-point Likert-type scale consisting of 25 questions. The scale aims to assess the overall level of adaptation of individuals with chronic diseases. The scale includes three subscales: physical adaptation, social adaptation, and psychological adaptation. Questions 1, 9, 10, 13, 14, 15, 16, 18, 22, 23, and 24 assess physical adaptation (minimum 11, maximum 55 points), questions 2, 3, 5, 7, 17, 19, and 25 assess social adaptation (minimum 7, maximum 35 points), and questions 4, 6, 8, 11, 12, 20, and 21 assess psychological adaptation (minimum 7, maximum 35 points). Items 5, 6, 12, 17, 19, 20, 24, and 25 are reverse-scored (5, 4, 3, 2, 1). The maximum score that can be obtained from the scale is 125, and higher scores indicate better adaptation to the disease. The Cronbach's alpha internal consistency coefficient of the scale was found to be 0.88.

Statistical analyses of the data obtained in the study were performed using SPSS v.19.0 Statistics software version (IBM Corp., Armonk, NY, USA). Parametric tests were used for scale data that followed a normal distribution, while non-parametric tests were used for data that did not meet the assumptions of normality. Descriptive statistics, independent samples t-test, Mann-Whitney U test, Kruskal-Wallis test, and Spearman correlation test were used as statistical methods. The level of statistical significance (p) was reported along with the respective tests and $p<0.05$ was considered as statistically significant.

RESULTS

Of the participants in our study, 53.7% were female (n=226) and 46.3% (n=195) were male, with a mean age of 75.21 ± 7.68. Among the participants, 48.9% (n=206) were in the age range of 65-74, 26.6% (n=112) were in the age range of 75-84, and 24.5% (n=103) were 85 years and older. A total of 65.5% of the participants (n=276) were married, while 16.9% (n=71) were living alone. Regarding education, 48% (n=202) of the participants had completed primary school, and all participants had health insurance.

The participants had an average duration of 16.54 ± 10.44 years of hypertension, and 81% (n=341) had other chronic conditions besides hypertension. The median number of daily medications used for their chronic conditions was four.

Regarding awareness, 97.1% (n=409) of the participants reported being informed about hypertension and its treatment, while 37.3% (n=157) stated that their families were also informed. Among the participants, 54.2% (n=228) believed that their families provided support in their treatment.

The mean systolic blood pressure (SBP) of the participants was 137.15 ± 20.38 mm Hg (minimum 92 mm Hg, maximum 206 mm Hg), and the mean diastolic blood pressure (DBP) was 81.25 ± 10.62 mm Hg (minimum 61 mm Hg, maximum 120 mm Hg). The distribution of blood pressure according to the 2019 Turkish Hypertension Consensus Report is presented in Table 1 (13). Participants with SBP under 120 mmHg and DBP under 80 mmHg were considered to have controlled blood pressure.

Table 1. Blood pressure levels of the participants

	n	%
Under control	34	8
Elevated blood pressure	125	29.7
Grade 1 hypertension	168	40
Grade 2 hypertension	94	22.3

The scores of the participants from the ACIS and its sub-dimensions are shown in Table 2. The mean score of adaptation to chronic diseases was found to be 87.04±9.77.

Table 2. Mean ACIS scores of the participants

	Min – Max	Mean ± Sd
ACIS	62-116	87.04±9.77
Physical adaptation	23-53	38.50±5.70
Social adaptation	16-47	25.10±3.08
Psychological adaptation	16-31	23.45±3.25

ACIS: Adaptation to Chronic Ilness Scale; Min: Minimum; Max: Maximum; Sd: Standart deviation

The socio-demographic and personal variables associated with the mean scores of adaptation to chronic diseases are presented in Table 3.

There was no significant relationship found between gender (p=0.77), duration since the diagnosis of hypertension (p=0.07), presence of chronic diseases other than hypertension (p=0.99), and the ACIS score. Similarly, no statistically significant relationship was observed between participants' knowledge of hypertension and its treatment and the ACIS score (p=0.05). However, it was observed that participants whose families were informed about their condition had higher ACIS scores (p=0.02).

Table 3. Mean ACIS scores of the participants according to different variables

	ACIS	Physical adaptation	Psychological adaptation	Social adaptation
Age				
65-74	89.04±9.95	39.73±5.55	23.79±3.45	25.53±3.20
75-84	84.93±9.14	37.36±5.69	22.94±2.81	24.62±2.76
85+	85.35±9.36	37.27±5.52	23.32±3.25	24.76±3.10
	p=0.001	**p<0.001**	p=0.121	**p=0.028**
Educational status				
Illiterate	73.80±6.99	31.20±5.08	20.03±2.10	22.56±2.52
Literate	86.44±8.84	37.13±5.21	24.06±2.41	25.34±5.10
Primary school	87.34±8.94	38.55±5.20	23.66±3.11	25.12±2.78
Secondary school	90.58±8.04	39.79±4.48	24.54±3.17	26.25±3.06
High school	89.06±10.10	40.22±5.44	23.29±3.51	25.54±2.76
University	88.26±10.05	40.08±6.22	23.42±3.35	24.76±2.66
	p<0.001	**p<0.001**	**p<0.001**	**p<0.001**
Marital status				
Single	84.29±10.97	36.17±6.16	23.29±3.72	24.82±2.24
Married	89.10±9.12	39.78±5.17	23.81±3.32	25.50±2.76
Widowed	82.80±9.69	36.00±5.83	22.56±2.86	24.24±3.70
Divorced	86.75±9.03	36.25±7.58	26.25±2.87	25.10±1.08
	p<0.001	**p<0.001**	**p=0.003**	**p<0.001**
Living alone				
Yes	81.40±9.24	34.76±5.95	22.52±2.94	24.16±2.79
No	88.19±9.49	39.26±5.34	23.64±3.29	25.29±3.11
	p<0.001	**p<0.001**	**p=0.016**	**p=0.003**
Has your family been informed about your illness and its treatment?				
Yes	88.62±9.04	39.96±4.90	23.59±3.28	25.07±3.18
No	86.11±10.09	37.63±5.96	23.36±3.24	25.12±3.03
	p=0.025	**p<0.001**	p=0.620	p=0.828
Does your family support you with your illness and treatment?				
Yes	89.19±9.62	39.75±5.30	23.97±3.24	25.45±3.45
No	84.51±9.36	37.01±5.80	22.82±3.17	24.68±2.54
	p<0.001	**p<0.001**	**p<0.001**	**p=0.007**

ACIS: Adaptation to Chronic Ilness Scale

DISCUSSION

The most common, disabling, and economically burdensome problems in a society are the most significant public health issues for that society. With the increasing elderly population, chronic diseases have become the most important public health problem. Hypertension, as a systemic disease that can lead to complications and is prevalent in the population, is an important chronic disease. In order to effectively manage chronic diseases, it is considered crucial for patients to actively participate in the management of their health. This can be achieved through patient education, support and motivation, and building trust between patients and the healthcare system and providers. Therefore, adherence to chronic disease management is important for both patients and healthcare professionals.

In our study, the proportion of participants with controlled blood pressure was found to be significantly lower compared to the literature (5, 14, 15). In the PatenT2 study conducted in our country in 2012 (5), it was reported that only 28.7% of hypertensive participants had their blood pressure under control. Furthermore, 50.9% had stage 1 hypertension, 15.3% had stage 2 hypertension, and 5.8% had stage 3 hypertension. The reason for the significant difference between our study and the literature is that previous studies considered blood pressure below 140/90 mm Hg as controlled, while in our study, participants with systolic blood pressure (SBP) below 120 mmHg and diastolic blood pressure (DBP) below 80 mmHg were considered as controlled, following the blood pressure target recommended for the elderly

according to the 2019 Turkish Hypertension Consensus Report (13).

In a study conducted on the quality of life of hypertensive patients, it was reported that as individuals age, their physical functioning and role, mental health, energy, social role, and sensory role scores decrease (17). The social and physical limitations that come with aging also affect the adaptation to chronic disease management. In primary care, the approach to elderly individuals allows for a more detailed and effective focus on social and physical limitations compared to other specialties. A comprehensive geriatric assessment in primary care enables the identification of various problems, classification of reserves and resilience, determination of necessary services for intervention, and development of a coordinated treatment plan through a multidisciplinary approach. The follow-up and treatment of chronic diseases can be carried out rapidly, reliably, affordably, and conveniently. The aim is to preserve functionality, ensure autonomy, and maintain the patient's quality of life at an optimum level. For all these reasons, necessary adjustments should be made in our healthcare system to increase the number of primary care physicians specializing in family medicine, improve the referral chain, and ensure that geriatric patients receive comprehensive and high-quality services at the primary care level, thus enhancing their adaptation to the disease.

There are studies in the literature that demonstrate the potential association between marital status and psychosocial adaptation (17, 18). In our study, a significant relationship was found between the participant's marital status and their scores on ACIS and its sub-dimensions, with the widowed group receiving lower scores. In a study by Erşan et al. (17), participants who were separated/divorced were found to have significantly higher levels of depression compared to those who were married. Similarly, in our study, it was determined that widowed individuals had significantly lower levels of adaptation compared to married individuals, which is consistent with the literature. This difference could be attributed to the stress caused by the loss of a spouse, lack of social and emotional support, and consequent difficulty in coping with stress.

There are studies in the literature that demonstrate the potential association between educational level and disease adaptation and adherence to treatment (19, 20). In a study conducted by Tokem et al. (19), it was found that illiterate individuals with hypertension had significantly lower levels of hypertension knowledge and adaptation compared to those who were literate or had completed school. Similarly, in our study, it was found that illiterate participants had lower levels of disease adaptation, which is consistent with the literature. This result may be attributed to higher-educated individuals having a better awareness of their condition, a better understanding of their disease and its treatment, and more related knowledge.

In our study, it was found that individuals living alone had significantly lower disease adaptation compared to those who did not live alone. This finding is consistent with the study conducted by Çam et al. (18), which also found that individuals living alone had lower psychosocial adaptation to the disease. This difference may be attributed to the limited social support experienced by individuals living alone. Additionally, the absence of a family member who can motivate the individual to adhere to non-pharmacological treatments such as diet and exercise may also contribute to the lower disease adaptation observed in those living alone. Increasing the number of active aging centers, where the elderly can socialize and engage in various activities, and encouraging individuals to spend time in these centers can provide social support to the elderly. This can facilitate coping with stress and promote more positive emotions among those who may feel lonely or depressed.

In a study investigating the contribution of family involvement in patient education to hypertension management, participants were divided into four groups: control group, family-oriented group, patient-oriented group, and patient and family-oriented group. After a four-month education program, the patient and family-oriented group showed significant improvements in medication adaptation, low-sodium diet adaptation, adaptation to medical appointments, and overall treatment adaptation (21). Similarly, a systematic review has indicated that educating patients and their families through various methods contributes to patient adherence (22). Consistent with these findings, our study also found that participants whose families were informed had higher disease adaptation. When families are knowledgeable about the disease, they can assist the patient in adhering to dietary recommendations and engaging in exercise. Feeling supported by their families, patients may experience better psychosocial well-being and demonstrate better adaptation to their condition. Barretto et al. (23) highlighted that many individuals with chronic illnesses view their families as the main source of support and security, and therefore, family organization and interactions directly impact treatment success in chronic diseases. The most common form of support has been related to the continuity of non-pharmacological treatment (23). A meta-analysis on social support and adaptation has also shown that individuals with strong family bonds have better adaptation (24). In our study, participants who perceived support from their families also had higher levels of adaptation. Taken together, these findings suggest that involving and educating families in the management process of the disease

and ensuring their support is crucial for improving individuals' adaptation to the disease.

Our study is a single-center study; therefore, the findings do not represent the entire country. Variability may be observed between regions due to sociocultural and economic differences. Since our study is cross-sectional, it cannot demonstrate changes in adherence over time. A longer-term prospective study could be more effective in evaluating hypertension adherence in elderly individuals.

CONCLUSION

Adherence is a complex process encompassing physical, psychological, and social dimensions. Our study determined that age, marital status, education level, living alone, informing families about the disease, and providing support to patients have various impacts on adherence to chronic illness management. The adherence levels of elderly individuals were found to be significantly low. Existing literature predominantly focuses on the adherence to medication. There is a need for more studies that specifically address patients' adherence to their diseases. Such studies would enable us to better understand patients and develop new strategies to enhance their adherence.

Conflict of Interest: No conflict of interest was declared by the authors.

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RESEARCH ARTICLE

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The Prevalence of Obstructive Sleep Apnea in Bariatric Surgery Patients

ABSTRACT

Objective: Obesity is one of the most important risk factors and also consequences of obstructive sleep apnea (OSA). Weight loss and positive airway pressure therapy are the main approaches in the treatment of OSA. In this study, it was aimed to evaluate the prevalence of OSA in obesity patients scheduled for bariatric surgery.

Methods: In the University Hospital Obesity Center, 141 consecutive patients who were candidates for bariatric surgery in 2015 were clinically evaluated preoperatively for sleep-related respiratory disorders. Preoperative polysomnographic examination was recommended to all cases.

Results: Of 141 bariatric surgery candidates with a mean age of 37±10 years, and 103 (73%) were female. The mean body mass index of the cases was 46.9±6.4 kg/m2. Among the major symptoms of OSA, snoring was present in 119 (84.4%), daytime sleepiness in 63 (44.7%) and witnessed apnea in 49 (34.8%) patients. OSA was detected because AHI>5/hour was found in 75.7% (84/111) of the patients who accepted the polysomnographic evaluation. 24.3% (27/111) of the cases who underwent polysomnography had non OSA, 29.7% (33/111) mild OSA, 17.1% (19/111) moderate OSA, and 28.8% (32 /111), severe OSA was detected. AHI was positively correlated with age (p=0.003), neck and waist diameter (p<0.001), and negatively correlated with percent of the forced vital capacity (p<0.001). In polysomnographic controls performed an average of 9 months after bariatric surgery, an average of 41.2% improvement in AHI was observed, compared to an average of 22.8% decrease in BMI.

Conclusions: OSA prevalence was found to be very high in bariatric surgery candidates. It was thought that polysomnographic examination should be performed before bariatric surgery not only in symptomatic cases but also in all cases. Bariatric surgery can help improve OSA.

Keywords: Obesity, Bariatric Surgery, Sleep Apnea, CPAP Therapy, Laparoscopic Sleeve Gastrectomy.

Obezite Cerrahisi Hastalarında Obstrüktif Uyku Apne Sıklığı

ÖZET

Amaç: Obezite, obstrüktif uyku apnesinin (OUA) en önemli risk faktörlerinden ve sonuçlarından biridir. Kilo verme ve pozitif hava yolu basıncı tedavisi OUA tedavisinde başlıca yaklaşımlardır. Bu çalışmada bariatrik cerrahi planlanan obezite hastalarında OUA prevalansının değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Üniversite Hastanesi Obezite Merkezi'nde 2015 yılında bariatrik cerrahi adayı ardışık 141 hasta, uyku ile ilişkili solunum bozuklukları açısından ameliyat öncesi klinik olarak değerlendirildi. Tüm olgulara ameliyat öncesi polisomnografik inceleme önerildi.

Bulgular: Yaş ortalaması 37±10 olan 141 obezite cerrahisi adayının 103'ü (%73) kadındı. Olguların ortalama vücut kitle indeksi 46,9±6,4 kg/m2 idi. OUA'nın majör semptomları değerlendirildiğinde; 119 (%84,4) hastada horlama, 63 (%44,7) hastada gündüz uyku hali ve 49 (%34,8) hastada tanıklı apne vardı. Polisomnografik değerlendirmeyi kabul eden hastaların %75,7 'sinde (84/111) AHİ>5/saat bulunması nedeniyle OUA saptandı. Polisomnografi yapılan olguların %24,3'ünde (27/111) OUA negatifdi, %29,7'sinde (33/111) hafif OSA, %17,1'inde (19/111) orta derecede OUA ve %28,8'inde (32/111) şiddetli OUA saptandı. AHİ ile yaş (p=0.003), boyun ve bel çapı (p<0.001) arasında pozitif, zorlu vital kapasite yüzdesi arasında negatif korelasyon (p<0.001) bulundu. Obezite cerrahisinden ortalama 9 ay sonra yapılan polisomnografik kontrollerde AHİ'de ortalama %41,2 iyileşme, VKİ'de ortalama %22,8 azalma gözlendi.

Sonuç: Obezite cerrahisi adaylarında OUA prevalansı oldukça yüksek bulunmuştur. Obezite cerrahisi öncesi sadece semptomatik olgularda değil tüm olgularda polisomnografik inceleme yapılması gerektiği düşünülmektedir. Bariatrik cerrahi OSA'yı iyileştirmeye yardımcı olabilir.

Anahtar Kelimeler: Obezite, Bariatrik Cerrahi, Uyku Apnesi, CPAP Tedavisi, Laparoskopik Sleeve Gastrektomi.

INTRODUCTION

Obstructive sleep apnea (OSA), the most common sleep breathing disorder, is a syndrome characterized by recurrent partial or complete collapses of the upper airway during sleep. OSA is common worldwide and is estimated to affect approximately 1 billion people globally, with a prevalence exceeding 50% in some countries (1).

Obesity is one of the most important risk factor and also consequences of OSA. OSA prevalence is very high in obese individuals and there is a high prevalence of obesity in patients with OSA. The pathophysiology of OSA is closely linked to obesity (2). Increased sleep collapsibility due to anatomical and/or functional disorders of the upper respiratory tract plays a key role in the pathogenesis of obstructive sleep apnea (2, 3). Obesity and especially central adiposity are strong risk factors for sleep apnea. Obesity may increase pharyngeal collapse through mechanical effects on pharyngeal soft tissues and lung volume and through central nervous system interacting signaling proteins (adipokines) that may affect airway neuromuscular control (3). Various behavioral, pharmacological, and surgical approaches to weight loss can improve patients with OSA, with differential effects on the mass and activity of regional adipose depots (3).

Numerous diseases are associated with both OSA and obesity, and these associations are clearly driven by complex mechanisms. OSA and its accompanying diseases and the mechanisms of these diseases show that obesity is one of the most important factors in OSA. Positive airway pressure (PAP) therapy, oral appliance therapy and some nose-throat surgeries are the main approaches in the treatment of OSA (3).

The fact that the multiple adverse health effects of severe obesity can be corrected by successful weight loss is the mainstay of obesity treatment. Bariatric surgery is applied to lose weight in patients who cannot lose weight with non-surgical methods. It is common among people with severe obesity that medical treatments to achieve sustainable weight loss fail. Indications for bariatric surgery are evolving rapidly, taking into account the severity of obesity as determined by BMI and co-existing conditions (4).

Bariatric surgery is relatively inexpensive when compared to the cost associated with severely obese inability to lose weight. As the popularity of bariatric surgery increases, its impact on diabetes, cardiovascular diseases and total mortality can be better documented (5, 6). The ultimate benefit of medical or surgical weight loss is related to the reduction of comorbidities, all cause mortality and increase in quality of life. Despite the successful implementation of non-surgical effective health management in the treatment of obesity, there is increasing evidence that bariatric surgery is more effective (7-9). A meta-analysis of bariatric surgery studies reported that weight loss ranged from 15% to 30%, depending on the specific surgical procedure performed, and decreased cardiovascular and overall mortality (10).

In this study, it was aimed to evaluate the frequency of OSA in obesity patients who will undergo bariatric surgery and the changes in the severity of the disease after weight loss in the postoperative period in patients with OSA.

MATERIAL AND METHODS

Study Population: All consecutive patients who were candidates for bariatric surgery (laparoscopic sleeve gastrectomy) in 2015 at Düzce University Hospital Obesity Center were clinically evaluated preoperatively in terms of sleep breathing disorders. In our center, laparoscopic sleeve gastrectomy is applied to all cases as bariatric surgery. All patients were questioned in detail in terms of OSA symptoms and Epworth Sleepiness Scale questionnaire was applied. In addition, concomitant diseases and regularly used drugs were noted. Ear, nose and throat (ENT) examinations, chest X-rays and spirometric tests were routinely performed in the preoperative period. Polysomnographic examination was recommended to all cases before surgery. Full polysomnography was performed in the laboratory all night in the patients who accepted. Positive airway pressure (PAP) titration was performed with full polysomnographic examination before bariatric surgery in patients with moderate and severe OSAS who had significant daytime sleepiness and/or accompanying cardiovascular risk factors. Symptomatic moderate and severe OSAS patients were treated with preoperative PAP for 8 weeks, as before all elective surgeries, and were carefully followed up in terms of complications related to OSAS in the postoperative period. It was planned to re-evaluate weight loss and OSAS status by polysomnography 6 months after surgery for patients who were found to have OSAS before bariatric surgery.

Our study was approved by the Duzce University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee (41/2014). The study was also supported by Düzce University as a Scientific Research Project (Project number: 2014.04.03.268).

Polysomnographic Sleep Study: All-night polysomnography (Philips Respironics Model: Alice-6 PSG, Germany) was performed in the laboratory in 111 consecutive patients who were candidates for bariatric surgery and accepted polysomnographic examination. Three-channel EEG (electroencephalography), 2-channel EOG (electrooculography), 1-channel chin EMG (electromyography), mouth and nose airflow (with thermistor and nasal cannula), thorax and abdomen movements, body position, snoring,

electrocardiography (ECG) and pulse oximetry recordings were made (> 6 hours). All records were scored manually on the computer according to the 2012 criteria of the American Academy of Sleep Medicine (AASM) (11). Patients with an apnea-hypopnea index (AHI) <5/hour were classified as no OSA, patients with AHI 5-15/hour were classified as mild OSA, patients with AHI 16-30/hour were classified as moderate OSA, and patients with AHI>30/hour were classified as severe OSA.

Statistical Analysis: Statistical analyzes were performed using the SPSS 15.0 program. In cases with OSA (+) and (-) candidates for bariatric surgery, clinical numerical parameters were compared with Student's t-test and categorical parameters were compared with chi-square test. Pearson correlation analysis was used to determine whether there was a correlation between the AHI and clinical parameters. P value <0.05 was considered statistically significant.

RESULTS

Of 141 bariatric surgery candidates with a mean age of 37±10 years, 38 (27%) were male and 103 (73%) were female. The mean body mass index of the cases was 46.9±6.4 kg/m2. Among the major symptoms of OSA, snoring was present in 119 cases (84.4%), daytime sleepiness was present in 63 cases (44.7%), and witnessed apnea was present in 49 cases (34.8%) (Figure 1).

OSA was detected in 84 (75.7%) of 111 subjects who underwent polysomnographic evaluation due to AHI above 5/hour (79 women, 32 men). 24.3% (27/111) of the cases who underwent polysomnography had nonOSA, 29.7% (33/111) mild OSA, 17.1% (19/111) moderate OSA, and 28.8% (32 /111), severe OSA was detected (Figure 2).

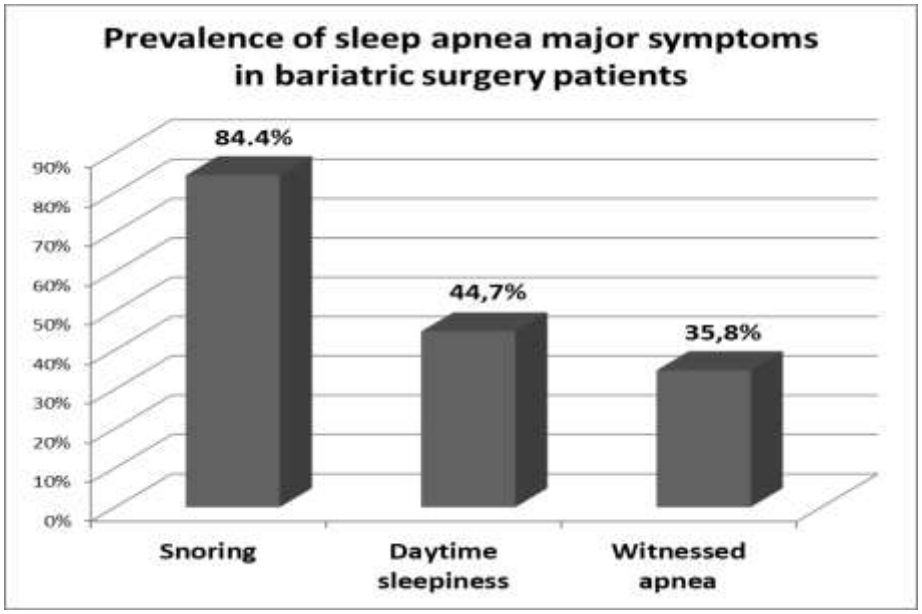

Figure 1. Prevalence of obstructive sleep apnea majör symptoms in bariatric surgery patients

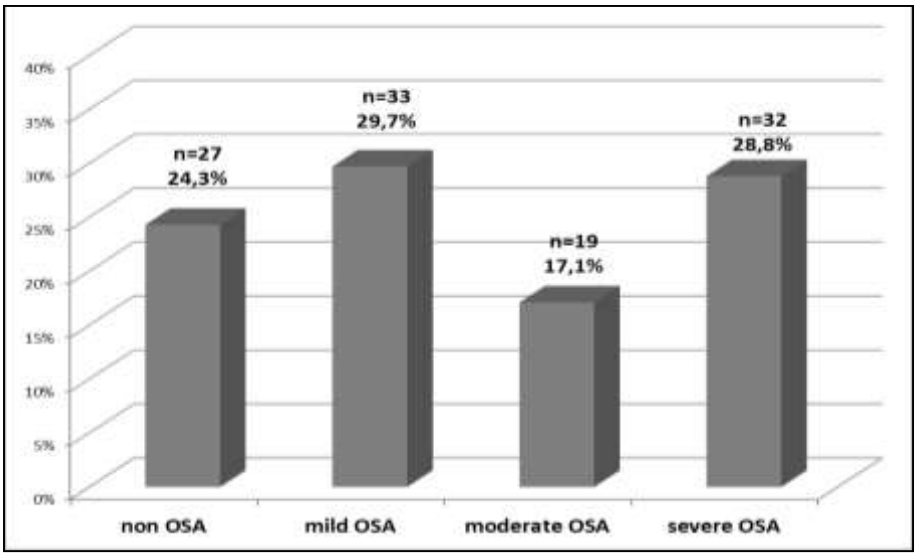

Figure 2. OSA severity in bariatric surgery patients

A coexistence of OSA and obesity hypoventilation syndrome was detected in 10 (9%) of the patients who underwent polysomnography. OSA was diagnosed by polysomnography at a statistically significantly higher rate in those with snoring, daytime sleepiness, and witnessed apnea than those without these symptoms (respectively 83%, 90.6%, 97.6% vs. 31.3%, 61.4%, 61.8%, p<0.001) (Table 1). The frequency of OSA was found to be significantly higher in male candidates for bariatric surgery than females (90.6% vs. 69.6%, p=0.027). In bariatric surgery candidates, the frequency of diabetes and hypertension in patients with OSA was found to be statistically significantly higher than in patients without OSA (Table 1).

Table 1. Comparison of some clinical parameters in bariatric surgery candidates according to OSA status

	OSA (+) **n (%)**	**OSA (-)** **n (%)**	***p***
Gender			
Female	55 **(69.6)**	24 (30.4)	***0.027***
Male	29 **(90.6)**	3 (9.4)	
Major seymptoms of OSA			
Snoring			
Yes	78 **(83.0)**	16 (%17.0)	***<0.001***
No	5 **(31.3)**	11 (68.8)	
Daytime sleepiness			
Yes	48 **(90.6)**	5 (9.4)	***<0.001***
No	35 **(61.4)**	22 (38.6)	
Witnessed apnea			
Yes	41 **(97.6)**	1 (2.4)	***<0.001***
No	42 **(61.8)**	26 (38.2)	
Diabetes mellitus			
Yes	30 **(88.2)**	4 (11.8)	***0.032***
No	49 **(68.1)**	23 (31.9)	
Hypertension			
Yes	27 **(93.1)**	2 (6.9)	***0.006***
No	52 **(67.5)**	25 (32.5)	
Hypothyroidism			
Yes	15 **(83.3)**	3 (16.7)	*0.267*
No	64 **(72.7)**	24 (27.3)	
Gastro-esophageal reflux			
Yes	26 **(78.8)**	7 (21.2)	*0.632*
No	66 **(72.2)**	23 (25.8)	
Asthma/COPD			
Yes	6 **(85.7)**	1 (14.3)	*0.675*
No	73 **(73.7)**	26 (26.3)	

OSA: obstructive sleep apnea; COPD: chronic obstructive pulmonary disease

In bariatric surgery candidates, the group with OSA was statistically significantly older. Epworth sleepiness scale value and sleep efficiency rate were significantly higher in OSA patients than in those without. There was no statistically significant difference between neck and waist diameter, smoking and pulmonary function test parameters between the groups with and without OSA in bariatric surgery candidates (Table 2).

AHI was positively correlated with age (p=0.003), neck and waist diameter (p<0.001), and negatively correlated with percent forced vital capacity (p<0.001), (Figure 3-6).

Table 2. Comparison of some clinical parameters in bariatric surgery candidates according to OSA status

	OSA (+) **Mean ± SD**	**OSA (-)** **Mean ± SD**	***p***
Age *(years)*	39 ± 9	33 ± 9	***0.009***
Body mass index *(kg/m^2)*	46.8 ± 5.5	45.4 ± 6.7	*0.281*
Neck diameter *(cm)*	42 ± 5	41 ± 4	*0.459*
Waist diameter *(cm)*	126 ± 14	118 ± 14	*0.059*
Smoking *(paket-yıl)*	7.2 ± 12.0	3.6 ± 6.3	*0.054*
FVC *(%)*	88 ± 14	89 ± 10	*0.764*
FEV1 *(%)*	88 ± 14	91 ± 10	*0.361*
FEV1/FVC *(%)*	83 ± 6	84 ± 5	*0.461*
Apnea Hypopnea Index	29.7 ± 26.6	2.6 ± 1.6	***<0.001***
Epworth sleepiness scale	7.8 ± 5.1	4.9 ± 4.7	***0.012***
Sleep efficiency *(%)*	80 ± 13	71 ± 14	***0.002***

OSA: obstructive sleep apnea; SD: standard deviation; FVC: forced vital capacity; FEV1: forced expiratory volume 1 second

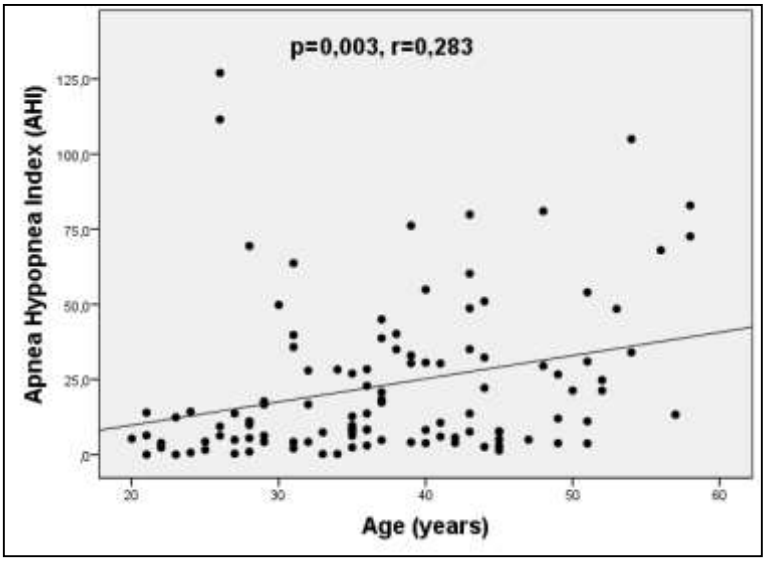

Figure 3. Correlation between apnea hypopnea index and age in bariatric surgery candidates

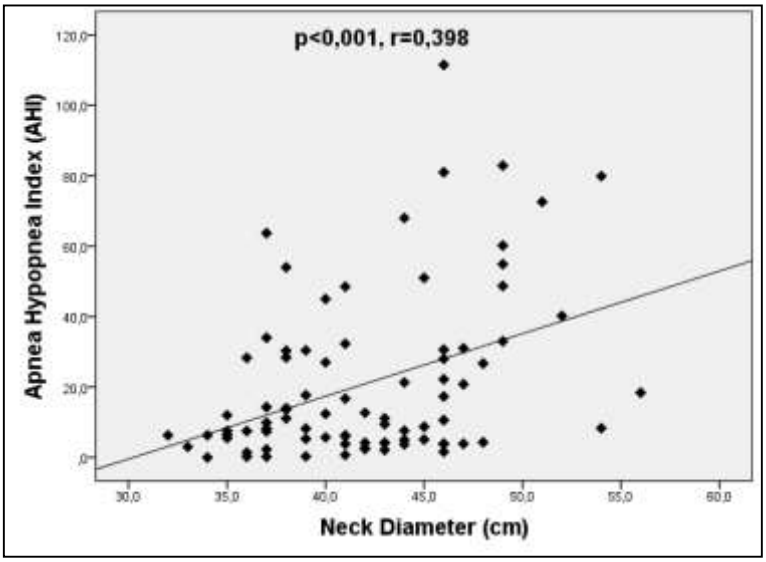

Figure 4. Correlation between apnea hypopnea index and neck diameter in bariatric surgery candidates

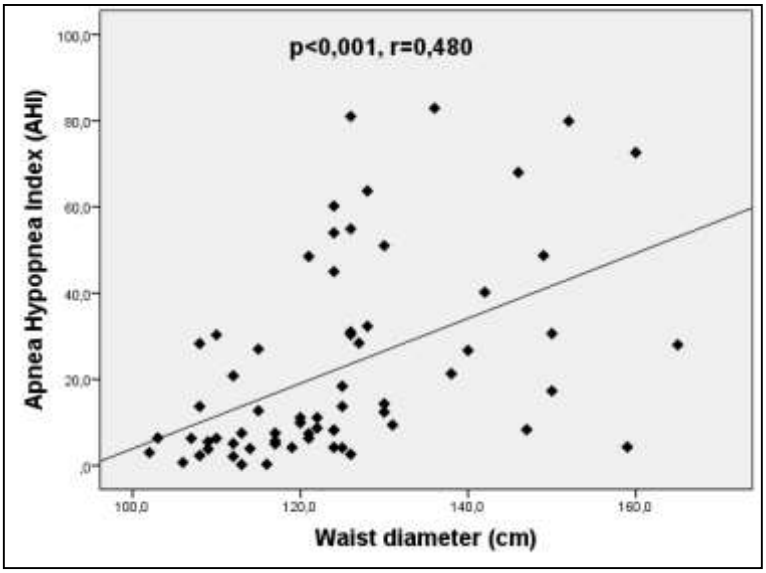

Figure 5. Correlation between apnea hypopnea index and waist diameter in bariatric surgery candidates

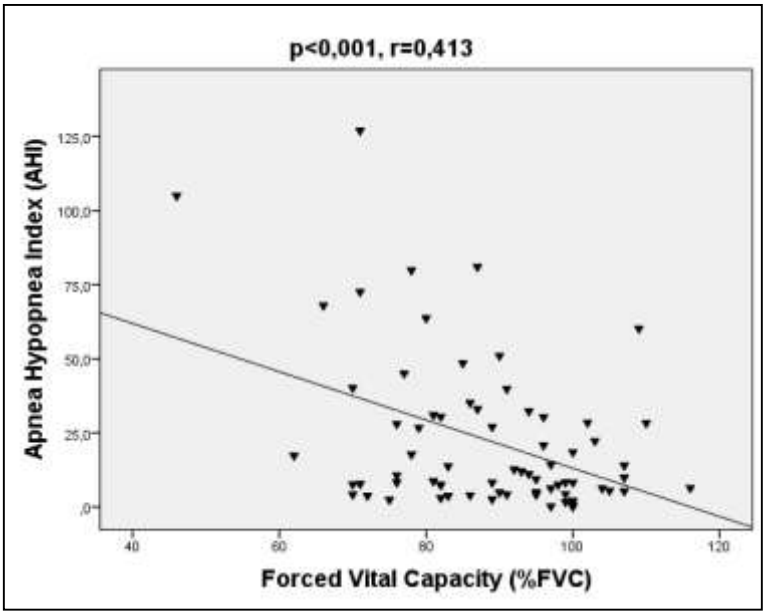

Figure 6. Negative correlation between apnea hypopnea index and FVC percentage in bariatric surgery candidates

Postoperative respiratory complication after bariatric surgery (laparoscopic sleeve gastrectomy) was not observed in any of the cases.

The changes in BMI and AHI values of 6 cases controlled after bariatric surgery (Laparoscopic sleeve gastrectomy) are shown in Table 3. In polysomnographic controls performed an average of 9 months after bariatric surgery, an average of 41.2% improvement in AHI was observed, compared to an average of 22.8% decrease in BMI.

Table 3. Change in AHI with control polysomnography of patients who lost weight after bariatric surgery

Case	Gender	Age (years)	BMI	BMI	Follow-up (months)	AHI	AHI	AHI reduction (%)
			Before	After		Before	After	
1	Female	40	47.7	36.7	8	8.2	4.9	41
2	Male	30	40.1	28.2	16	35.1	12.1	65
3	Female	26	42.1	35.2	6	25.9	18.1	30
4	Female	49	44.1	38.3	9	111.2	68.4	38
5	Female	43	62.1	44.2	8	72.3	56.6	22
6	Female	37	48.2	38.4	8	17.1	8.4	51
Means		**37.5**	**47.4**	**36.6**	**9**	**44.9**	**28.1**	**41.2**

BMI: body mass index (kg/m2); AHI: apnea hypopnea index/hour

DISCUSSION

As a result of this study, the prevalence of OSA in bariatric surgery candidates was found to be very high (75.7%). More importantly, nearly half of the cases had clinically significant moderate and severe OSA (45.9%). Moreover, OSA was present in at least 30% of patients having no major symptoms. Although all patients were obese, the severity of OSA increased as waist and neck circumferences increased. Again, advanced age was found to be an important factor increasing the prevalence of OSA in bariatric surgery candidates. It was determined that there was a significant improvement in AHI in patients with OSA who lost weight after bariatric surgery and had polysomnographic control.

In previous studies in bariatric surgery candidates, the frequency of OSA was reported to be between 77% and 96.7% (11-13).

Although the presence of major symptoms was found to be a significant indicator for the presence of OSA in the clinical evaluation for OSA in this study, the prevalence of OSA detected by polysomnography was much higher than the incidence of clinical major symptoms. Previous clinical studies have also shown a high prevalence of OSA in patients with obesity, despite the absence of patient-reported symptoms (14).

It has been reported that documentation of OSA and initiation of treatment before bariatric surgery can minimize possible complications of OSA in the postoperative period (15).

Based on this study, we recommend routine polysomnographic evaluation of all patients undergoing bariatric surgery. Prior to bariatric surgery, encouraging patients to lose 5-6 kilos with a low-calorie liquid diet and applying PAP therapy for at least 4-8 weeks before surgery in patients with moderate and severe OSA were routinely performed in this study. These two measures contributed to subjective improvement of OSA before surgery and minimizing pulmonary complications after surgery. In this study, postoperative respiratory complication after laparoscopic sleeve gastrectomy was not observed in any of the cases.

Our data show that weight loss obtained by obesity surgery provides clinical and polysomnographic improvement to morbid obese patients with OSA. Advantages include AHI reduction, reducing or termination of CPAP therapy, and the healing of the Epworth Sleepiness Scale (ESS) scores, which reflect the healing of daytime sleepiness. Following bariatric surgery, very few patients have entered into the polysomnographic evaluation at the end of an average follow -up of 9 months. Although the BMI values (average 36.6) in control cases are still high, even an average of 22.8% weight loss rates in BMI have caused an average improvement in an average of 41.2 %in AHI. However, in control cases, the average AHI level (28.1) is still above clinical desired levels.

Haines et al. OSA was found in 289 (83%) of 349 patients with preoperative polysomnography. Postoperative polysomnography was performed in 101 patients, and the mean AHI index (RDI) decreased from 51±4 to 15±2 at a median 11 months. ESS score decreased from 10±1 to 6±1 after 3 months. These results are consistent with the results of our study. However, the follow-up period in the study was longer, resulting in a greater reduction in AHI compared to our study (16). Similar improvements in OSA have been reported after bariatric surgery in many other studies (17-19).

Healing of sleep apnea is related to weight loss and reduction of upper airway adipose tissue. Reduction in visceral adiposity leads to improved diaphragm motion and improved ventilation and oxygenation (20). It is known that pro-inflammatory cytokine levels such as interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α) increase in patients with sleep apnea and obesity. Bariatric surgery leads to a decrease in IL-6 and other systemic inflammatory markers, and an increase in the anti-inflammatory IL-8 cytokine (21). Soluble TNF-α receptor 2 level has been reported to be an independent predictor of the development of sleep apnea and decreased after bariatric surgery (22).

One of the key observations in the Varela et al studies was that improvement in OSAS began immediately after surgery, before the desired level of weight was lost 23]. Similar findings were also reported by Haines et al. (16). The potential for improvement in OSA following bariatric surgery can be explained by two main factors. Effects associated with weight loss (reduced mechanical force on the cervical region, upper airway and diaphragm) and metabolic effects independent of weight loss. Ashrafian et al. suggested that metabolic surgery improves type 2 diabetes mellitus, insulin resistance, and metabolic syndrome through the BRAVE effect (bile flow alteration, restriction of stomach size, anatomical intestinal reorganization and altered nutrient flow, vagal manipulation and enteric bowel hormone modulation) (23). Since OSA and metabolic syndrome trigger each other, improvement in metabolic syndrome will lead to early recovery of OSA (24).

Almost all of the bariatric surgery and OSA studies showed a decrease in both AHI and BMI in the early period. In many studies with relatively short follow-up times, it was reported that the postoperative AHI was reduced to less than 20/hour (25). This finding may be explained by the fact that the subjects in these studies were relatively younger people with milder forms of OSA. Conversely, there are studies showing that the longer the follow-up, the greater the likelihood of OSA relapse (26). In the Feigel-Guiller et al study, a significant decrease in AHI was observed from 56.5/hr to 31.5/hr at 12 months, followed by an increase to 40.7/hr at 3 years (27).

One systematic review reported recurrence of OSA in the following years, possibly due to causes other than weight gain (26). Most studies suggest that weight loss continues in the short/medium term (1-2 years), and after this period, the probability of recurrence of OSA is higher. Therefore, the results may be inconsistent (25). Prospective studies with longer follow-up periods are needed.

Although there was no weight loss at the targeted level after surgical intervention in our study, there was significant improvement in AHI. However, the mean AHI score was still well above the target level. Since OSA is a disease with multiple risk factors, there may be permanent structural changes in the airways and/or central nervous system structures that cannot be reversed by bariatric surgery, despite good post-operative weight loss. This suggests that patients should be followed up regularly after bariatric surgery and polysomnographic controls should be performed when necessary.

There are some limitations in our study. The number of patients who had control

polysomnography after bariatric surgery is very small. In addition, the short follow-up period of the patients and the postoperative polysomnography before the target BMI is reached are another handicap. Positive results reported in short-term studies may be affected by concurrent short-term behavioral changes, such as increased exercise and healthy eating. Post-surgery weight loss is gradual, with patients usually achieving their lowest weight 12-24 months after surgery. However, after successful weight loss and improvement in quality of life following bariatric surgery, patients are reluctant to undergo overnight polysomnography. We need to follow these patients longer to document long-term outcomes after surgery.

In addition, since obesity, not OSA, was the predominant medical condition in this study, generalizing the results to the entire population of OSA patients may be objectionable.

CONCLUSION

As a result of the study, it was thought that all patients who will undergo bariatric surgery should be evaluated in detail in terms of sleep breathing disorders in the preoperative period and preoperative polysomnographic examination should be performed not only in symptomatic patients but also in all patients.

Bariatric surgery may also help improve clinical symptoms in patients with OSA, as well as AHI. Targeted weight loss may not be achieved in all patients after bariatric surgery, and the improvement may not be at the same level in all patients with OSA. Therefore, it was thought that the patients should be followed for a long time in terms of OSA in the postoperative period.

More randomized controlled studies with well-standardized and long follow-up are needed to reliably confirm the effects of bariatric surgery on OSA.

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethics committee approval was received for this study from the ethics committee of Duzce University (2014).

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare no competing interests.

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My manuscript has no associated data

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RESEARCH ARTICLE

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A Critical Issue for Primary Care Practice: Knowledge and Attitudes of Family Physicians Regarding Levothyroxine Use

ABSTRACT

Objective: Accurate management of hypothyroidism, which is one of the common reasons for referral to primary care, is critically important issue. This study aims to measure the knowledge and attitudes of family physicians (FPs) regarding the use of levothyroxine, which is the main pharmacological agent in the treatment of hypothyroidism.

Methods: This prospective and descriptive study was performed on 102 physicians from family health centers in Şanlıurfa province central districts. The researchers created a questionnaire consisting of eight questions; seven of which were multiple choices and one was open-ended, by scanning the guidelines and literature. Data were obtained by face-to-face interview technique.

Results: Of the participants, 21 (20.6%) were female and 81 (79.4%) male physicians, and the mean age of the participants was 36.9±8.0 (28-66) years. The work duration as a FP was 6.1±3.3 years. Sixteen (15.7%) of the participants reported that they had never prescribed levothyroxine. Two-thirds of them correctly answered the relationship between levothyroxine absorption and food intake, and 36.3% correctly answered that there would be a difference in absorption between different levothyroxine formulations. However, the rate of correct answers to the question of how to start hypothyroidism treatment in patients over 60 years of age or with coronary artery disease was quite low.

Conclusions: The results of this study revealed that FPs in Sanliurfa central districts do not have adequate knowledge about the use of levothyroxine for treatment of hypothyroidism, and they need effective training on this vital issue.

Keywords: Attitude, Hypothyroidism, Knowledge, Levothyroxine.

Birinci Basamak Uygulamaları İçin Kritik Bir Konu: Aile Hekimlerinin Levotiroksin Kullanımına İlişkin Bilgi ve Tutumları

ÖZET

Amaç: Amaç: Birinci basamağa sık başvuru nedenlerinden biri olan hipotiroidinin doğru yönetimi kritik öneme sahip bir konudur. Bu çalışma, aile hekimlerinin hipotiroidi tedavisinde temel farmakolojik ajan olan levotiroksin kullanımına ilişkin bilgi ve tutumlarını ölçmeyi amaçlamaktadır.

Gereç ve Yöntem: Prospektif ve tanımlayıcı tipte olan bu çalışma, Şanlıurfa ili merkez ilçelerdeki aile sağlığı merkezlerinde görev yapan 102 aile hekimi üzerinde yapılmıştır. Araştırmacılar tarafından kılavuzlar ve literatür taranarak yedisi çoktan seçmeli ve biri açık uçlu sekiz sorudan oluşan bir anket oluşturuldu. Veriler yüz yüze görüşme tekniği ile elde edildi.

Bulgular: Katılımcıların 21'i (%20,6) kadın, 81'i (%79,4) erkek hekimdi ve yaş ortalaması 36,9±8,0 (28-66) idi. Aile hekimi olarak çalışma süresi 6,1±3,3 yıldı. Katılımcıların 16'sı (%15,7) hiç levotiroksin reçete etmediğini bildirdi. Üçte ikisi levotiroksin emilimi ile gıda alımı arasındaki ilişkiyi, %36,3'ü ise farklı levotiroksin formülasyonları arasında emilimde bir fark olup olmadığı sorusunu doğru yanıtladı. Ancak 60 yaş üstü veya koroner arter hastalığı olan hastalarda hipotiroidi tedavisine nasıl başlanacağını bilme oranı oldukça düşüktü.

Sonuç: Bu çalışmanın sonuçları, Şanlıurfa merkez ilçelerinde çalışan aile hekimlerinin hipotiroidi tedavisinde levotiroksin kullanımı konusunu yeterince bilmediklerini ve bu hayati konuda eğitime ihtiyaç duyduklarını ortaya koymuştur.

Anahtar Kelimeler: Levotiroksin, Bilgi, Tutum, Hipotiroidi.

INTRODUCTION

Hypothyroidism can seriously harm many systems and organs, notably the cardiovascular system, if it is not treated properly (1) and so accurate management of hypothyroidism, which is one of the common reasons for referral to primary care is a critically important issue for health of individuals. Today, orally administered levothyroxine (LT4) is accepted as the standard treatment for hypothyroidism and it has become the most commonly prescribed drug worldwide. However, some points should be considered in order to get the maximum benefit from the use of levothyroxine (2, 3).

In recent years, two new formulations of levothyroxine, soft gel and liquid, have been used in addition to the tablet form in some countries (4). It has been reported that the use of these different formulations (brand name or generic) has different effects on serum TSH values (5). The bioavailability of a drug is closely related to how the drug is used by the patient as well as its properties. How it is stored and what the patient eats and drinks affect the absorption of LT4. It is recommended to take it as a single dose in the morning, at least half an hour before breakfast (if possible, one hour before). It should not be exposed to sunlight, and the ambient temperature where it is stored should be between 20-25 °C (6). It is a forgotten point that some agents such as calcium and iron preparations and proton pump inhibitors (PPI), which are frequently prescribed in clinics, inhibit the absorption and bioavailability of LT4 when used simultaneously (7).

In the elderly and people with ischemic heart disease, it is necessary to start with a low dose of LT4 and increase it gradually (5). FPs are expected to have sufficient knowledge and appropriate attitude to advise patients on the necessary rules for patients to get the maximum benefit from LT4 treatment.

Although hypothyroidism is a common and important clinical disorder in primary care practice (8) it is seen that there are not enough studies in the literature evaluating the attitudes and knowledge of primary care physicians regarding levothyroxine administration. Precisely for this reason it is aimed to raise awareness about this critical issue in this study.

MATERIAL AND METHODS

The study was approved by the Harran University Rectorate Clinical Research Ethics Committee on January 13, 2020 with session 01 and decision numbered 05.

The universe of the study is defined as the FPs (total n=621) who were working in family health centers in Şanlıurfa province central districts. Sample size was calculated with G* power 3.1.9.7 program (effect size=0.30, alpha=0.05 and power 0.85) and it was determined as 93. The study was carried out with 10% more of this sample size (n= 102 FP).

In order to determine the knowledge and attitudes of the participants regarding the LT4 application, a questionnaire consisting of eight multiple-choice and one open-ended questions was prepared by the researchers by scanning the guidelines and literature. Additionally, their age, gender, the number of years of practice as a physician, the duration for which they had served as FPs, and the frequency of LT4 administration (per week) prescribed by them were recorded.

All of the participants were explained about the purpose of the study and that their personal data would not be shared and than the consent of the participating physicians were obtained at the beginning and the data were obtained by a face-to-face survey method. 102 (16.9%) FPs out of 621 FPs gave consent to participate in this study.

3 groups were determined according to their working hours as FPs. Group 1 defined the physicians who had a working experience of 1-5 years, Group 2 ; 6-10 years, and Group 3 ; 11 years or more of work experience.

Statistical Analysis: Statistical analyses were performed by using Statistical Package for the Social Sciences (SPSS Inc; Chicago, IL, USA) version 22.0 software. The categorical data were presented as n (%), while other data were presented as mean ±SD (min-max). The categorical data between groups were compared using the Chi-squared test, while continuous data were compared using Student's t-test. All differences between groups were considered to be statistically significant at $p < 0.05$.

RESULTS

The study was conducted with 102 FPs who gave consent to participate. Of the participants, 21 (20.6%) were female, 81 (79.4%) were male, and the mean age was 36.9 ±8.0 (28-66) years.

Participants had been practicing medicine for 10.3 ±7.0 (1-36) years and had been working as FPs for 6.1 ±3.3 (1-15) years. Before working in the family health center, 45 (44.1%) participants worked in other health centers, 46 (45.1%) in emergency services, and 10 (9.8%) worked in private clinics. Sixteen (15.7%) of them never prescribed levothyroxine.

Participants' weekly LT4 prescribing rates were; 18 (17.6%) once a week; 21 (20.6%) twice a week; 31 (30.4%) three-nine per week; 16 (15.7%) 10 or more times per week (Table 1).

Table 1. Distribution of physicians according to the number of prescriptions per week

Number of prescriptions per week	Number of physicians n (%)
0	16 (%15.7)
1	18 (%17.6)
2	21 (%20.6)
3	11 (%10.8)
4	8 (%7.8)
5	10 (%9.8)
7	2 (%2.0)
10	11 (%11.8)
12	1 (%1.0)
15	2 (%2.0)
20	1 (%1.0)
30	1 (%1.0)

When the participants were asked how to start hypothyroidism treatment for someone below 60 years who does not have coronary artery disease, 40 (39.2%) of them answered as “the full planned dose can be started”, and 27 (26.5%) as "I start half of the planned dose and then switch to the full dose after a week".

How is the treatment started for hypothyroidism in someone over 60 or with coronary artery disease were asked and 18 (17.6%) participants replied as, “I start at 12.5/25 mcg and increase by 12.5 mcg once a week”.

When we asked the participants, “What is the best time to use levothyroxine?”, 73 (71.6%) participants answered, "In the morning on an empty stomach".

The relationship between levothyroxine and food intake was asked and 67 (65.7%) of the participants answered as “Absorption decreases with satiety”.

When the participants were asked, “If you think levothyroxine should be used on an empty stomach, how long should the patient fast after taking the drug?”, 69 (67.6%) physicians answered as, "half an hour to an hour".

To the question “What do you think about the formulations of levothyroxine available in the market?", 37 (36.3%) of them gave the answer "Their absorption is different, so it is necessary to continue with the same formulation if possible".

It was asked how the storage conditions of the drug should be. 65 (63.7%) of the participants answered, “below 25 °C and in its box”.

The percentage distributions of multiple-choice questions and their answers are shown in Table 2.

Table 2. Rates of answers given to multiple choice survey questions.

Questions	Answers and rates (%)
How do you start hypothyroidism treatment in someone under 60 years of age who does not have coronary artery disease?	• Planned full dose can be started (39.2%) • I start half of the planned dose, I switch to the full dose a week later (26.5%) • I start at 12.5/25mcg, increase by 12.5mcg once a week (5.9%) • I do not want to answer / I do not know (28.4%)
How do you begin treatment for hypothyroidism in someone over 60 or with coronary artery disease?	• Planned full dose can be started (9.8%) • I start half of the planned dose; I switch to the full dose after a week (30.4%) • I start at 12.5/25mcg, increase by 12.5mcg once a week (17.6%) • I do not want to answer / I do not know (42.2%)
What do you think is the best time to use levothyroxine?	• In the morning on an empty stomach (71.6%) • After meal (12.7%) • Any time during the day (11.8%) • At bedtime (3.9%)
What do you think is the relationship between levothyroxine and food intake?	• Absorption decreases in hunger (14.7%) • Absorption decreases in satiety (65.7%) • Absorption does not change in hunger and satiety (19.6%)
If you think it should be used on an empty stomach, how long should be stay fasted after taking the drug?	• Can be eaten immediately (11.8%) • Half to an hour (67.6%) • At least two hours (20.6%)
What do you think of the oral formulations available in the market?	• Absorption is different, so it is necessary to continue with the same if possible (36.3%) • They all have the same absorption, so whichever is available (33.3%) • No idea (30.4%)
Under what conditions do you think this medicine should be stored?	• In the refrigerator (2%) • On the refrigerator door (10.8%) • Since it is not affected by heat and light, it can be stored under any conditions (23.5%) • Below 25°C and in the box (63.7%)

Finally, the participants were told that some commonly used drugs (eg, cholestyramine) may impair the absorption of levothyroxine and that there should be at least 2-4 hours between the use of two drugs, and they were asked to write what they knew about these drugs. 79 of the participants (77.5%) could not answer this question. The most common response was 'PPI' (21.5%), followed by 'calcium preparations' (5.8%).

The question, "How do you start hypothyroidism treatment in someone under 60 years of age who does not have coronary artery disease?", was answered by a significantly lesser number of physicians in Group 3 26 (76.4%), participants in Group 1, 22 (73.3%), participants in Group 2, and 19 (50.0%) participants in Group 3 (p=0.028).

The question, "What do you think of the oral formulations that are commercially available?", was answered by a significantly lesser number of physicians in Group 3. The rate of the answers were as 15 (44.1%) participants in Group 1, 11 (36.7%) in Group 2, and 11 (28.9%) participants in Group 3 (p = 0.016). No significant difference was found for the other answers in the three groups (Table 3).

Table 3. Distribution of the rate of correct answers given to the questions according to the groups.

Questions and correct answers	Group 1 (n=34)	Group 2 (n=30)	Group 3 (n=38)	p
Question How do you start hypothyroidism treatment in someone under the age of 60 who does not have coronary artery disease?" **Answer** "The planned full dose can be started" or "I start half the planned dose; I switch to the full dose after a week"	26 (%76.4)	22 (%73.3)	19 (%50.0)	0.028
Question "How do you start treatment for hypothyroidism in someone over 60 or with coronary artery disease?" **Answer** "I start at 12.5/25mcg, increase by 12.5 mcg once a week"	4 (%11.7)	6 (%20.0)	8 (%21.1)	0.328
Question What do you think is the best time to use levothyroxine?" **Answer** "Morning on an empty stomach"	26 (%76.4)	29 (%96.6)	27 (%71.1)	0.732
Question "What do you think is the relationship between levothyroxine and food intake?" **Answer** "Absorption decreases in satiety"	23 (%67.6)	20 (%66.7)	24 (%63.2)	0.051
Question "If you think it should be used on an empty stomach, how long should you fast after taking the drug?" **Answer** "Half to an hour"	21 (%61.7)	25 (%83.3)	23 (%60.5)	0.186
Question "What do you think of the oral formulations that are commercially available?" **Answer** "Their absorptions are different, so it is necessary to continue with the same if possible"	15 (%44.1)	11 (%36.7)	11 (%28.9)	0.016
Question "In what condition do you think this drug should be stored?" **Answer** "Under 25ºC and in the box"	17 (%50.0)	24 (%80.0)	24 (%63.2)	0.301

** Group 1; 1-5 years, Group 2; 6-10 years and Group 3; 11 years work experience.*

DISCUSSION

Hypothyroidism is an important disease that is a frequent reason for referral to primary care physicians. Several studies have investigated the management and treatment of hypothyroidism in patients (9-14). Studies on the knowledge and attitudes of physicians, who play an important role in the follow-up and treatment of patients, are frequently conducted on pregnant women (15, 16) In this study, the knowledge and attitudes of FPs regarding the use of levothyroxine were emphasized and the training needs on this subject were revealed.

In the study of Negro et al., on the management of thyroid diseases by General Practitioners (GP), 122 of 622 physicians participated in the study with a rate of 19.6% (17). In this study, 102 out of 621 physicians participated (participation rate was 16.4%), and the participation rate was slightly lower than that in the abovementioned study.

In a study by Askari et al. on the level of knowledge of physicians regarding thyroid disorders in pregnant women, 41.4% of the participants were male (16). In our study, 79.4% of the participants were male.

In a study by Hussien and Eldin on the knowledge and attitudes of primary care physicians regarding thyroid disorders, the mean age of the physicians was 34 ±7.8 years, and the mean working duration was 6.8 ±5 years (18). In a quantitative study conducted by Dew et al. on the knowledge of healthcare professionals regarding hypothyroidism, the age of the participants ranged from 25 to 60 years, which was similar to the age range in this study (19). In the study by Askari et al., the mean age of the physicians was 37.8 ±7.6 years (16) smilar to this study (36.9±8.0 years). Work experience as a FPs was found to be 6.1±3.3 years.

About 62-82% of levothyroxine is absorbed within 3 h, mainly from the duodenum and jejunum (7, 20). Maximum absorption occurs on an empty stomach. Levothyroxine intake with food can disrupt thyroid hormone regulation (5, 20). Thus, T4 preparations are recommended to be administered as a single dose, preferably with a glass of water, on an empty stomach (6) In this study, the participants were asked the best time to take levothyroxine, and most of the participants correctly answered as "In the morning on an empty stomach". When they were asked about the relationship between levothyroxine and food, two-thirds of the participants gave the correct answer which should be Absorption decreases with satiety". The participants were also asked about the duration of fasting after taking the drug. For optimal absorption, patients are recommended to take levothyroxine at least 0.5 to 1 h before breakfast (6, 20). Most of the participants answered this question correctly.

Levothyroxine should be stored at 25 °C in a box, away from light and moisture (20). More than half of the physicians answered the question about the storage conditions of levothyroxine correctly.

Levothyroxine is available in tablet, capsule, intravenous, and liquid forms (5, 21). Two different companies in Turkey have formulations in tablet form. Although the contents are the same, the absorption of different oral formulations might be different (2). The participants were asked for their opinion on the tablet forms available in the market. Approximately one-third of the participants correctly answered that the absorption of different formulations is different, and therefore, it is necessary to continue with the same one if possible. This question was answered by a few of Group 3 physicians, which included those with a work experience of 11 years or more. Physicians need to follow the developments in the field of medicine to administer the best treatment possible to the patient. We argue that these results reflect the need to continue education after graduating on the subject to be updated regarding the latest advancements and trends in the field.

In the study by Dew et al., healthcare professionals stated that hypothyroidism is easy to manage, but GPs and nurses generally have insufficient knowledge about drug interactions and levothyroxine pharmacokinetics (19). It has been reported that the absorption of thyroid hormones may be affected by some agents such as calcium, cholestyramine, sucralfate, and ferrous sulfate. Some antacids containing aluminum hydroxide also have effects on absorption (7, 22). In this study, the participants answered that drugs, such as PPI and calcium preparations, could impair levothyroxine absorption. Since most of the physicians did not give answer this question, it can be assumed that they do not have sufficient knowledge about drug interactions.

In a study by Serin et al., patients were asked about the foods and drugs that interact with levothyroxine, and 86% stated that they were unaware. The researchers also found that approximately 30% of iron and PPI were used along with levothyroxine (23). In the study by Dew et al., healthcare professionals stated that the incorrect administration of levothyroxine was the main reason for inadequate treatment (19). The knowledge of primary care physicians regarding drug interactions is very important in informing and educating patients for treating diseases effectively.

In the study by Dew et al., doctors and nurses were aware of the cardiac complications associated with rapid administration of levothyroxine to the patient (19). In the study by Askari et al., the lowest scores were related to iodine requirements and complications of thyroid disorders, while the highest scores were related to the questions about the diagnosis (16). Gibbons et al. evaluated the knowledge of physicians for diagnosing and managing subclinical hypothyroidism in a qualitative study involving GPs. They reported that there is considerable variation in how GPs perceive subclinical hypothyroidism and their knowledge of the disease. They stated that this variation was due to the uncertainty in the symptoms and prognosis of subclinical hypothyroidism and the variation in recommendations regarding treatment (24). In this study, 39.2% of the participants correctly answered the question on how to start hypothyroidism treatment in individuals below 60 years without coronary artery disease, and 17.6% correctly answered the question on how to start hypothyroidism treatment in individuals over 60 years or with coronary artery disease. When the answers were evaluated according to the groups, the lowest rate of the correct answer was given by the participants in Group 3, who had the longest work experience (11 or more years).

A study that evaluated the level of knowledge regarding thyroid disorders in primary care found that pre-training information was insufficient in GPs and FPs. The knowledge level of internists was found to be higher than that in GPs and FPs. The answers given to the information questions after being educated changed significantly and educating doctors to detect and manage thyroid disorders in primary care is necessary (18). Askari et al. reported that doctors in Iran have insufficient knowledge about the management of thyroid disorders in pregnant women [16]. In a study conducted in Turkey, physicians were found to have insufficient and/or incorrect information on thyroid disorders in pregnant women. While endocrinologists had the highest scores in each department, FPs had higher scores than obstetricians (15). Negro et al. reported that, most of the GPs (72.1%) performed preliminary examinations before referring the patient with suspected thyroid dysfunction to a specialist, and the level of knowledge of the physician determined their attitude toward patient management (17). In this study, however, a comparison could not be made because of the limited number of specialist physicians.

It can be said that adequate control could not be achieved in patients with hypothyroidism using levothyroxine according to some studies on this issue (25, 26)

A study on the management of primary care physicians' use of levotroxine also revealed that participants had a proactive attitude in therapy and that they deviated from the recommendations in the guidelines for various reasons (27).

CONCLUSION

We believe that the results of this study will contribute to raising awareness about the deficiencies in the management of hypothyroidism therapy by levothyroxine in primary care. For improving public health, FPs who encounter chronic diseases most frequently, should follow current guidelines and publications on the management of these diseases. Effective training programs for FPs and for patients to ensure the correct application of standard protocols are the key for effective treatment of hypothyroidism.

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RESEARCH ARTICLE

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Comparison of Early Versus Late Urethral Catheter Removal After Transurethral Resection of the Prostate in Patients with Benign Prostate Hyperplasia

ABSTRACT

Objective: Transurethral resection of the prostate (TURP) is considered the standard in the surgical therapy of lower urinary tract symptoms related to benign prostate hyperplasia (BPH). However, there is no consensus on the timing of catheter removal. In this study, we aimed to compare the long-term effects of early and delayed removal of urethral catheters who underwent TURP.

Methods: We prospectively analyzed a total of 91 patients who underwent TURP. Patients were randomized into two groups; the early (postop 1st-2nd days) and delayed (7th day) removal of the urethral catheter. After the surgery in 1, 3, and 6th months, we evaluated all patients regarding treatment success. In addition, international prostate symptom score (IPSS), quality of life (QoL), maximum flow rate, postvoid residual urine volume, and morbidities (hematuria, infection, urethral stricture, irritative symptoms, need for re-operation) were assessed at all visits.

Results: After TURP, there was no statistical difference in urodynamic parameters, complications, IPSS, and QoL in both groups. Only in the 3rd-month, the maximum flow rate was higher in favor of the early group. Despite similar results in both groups, strictures occurred earlier in the early group than delayed group (respectively 1 and 3 months).

Conclusions: These results suggest that there are no differences in efficacy and complications in groups of early or delayed urethral catheter removal after TURP. The results of long-term studies with large series should be awaited to reach a more definite conclusion. We have tried to shed light on a topic without consensus on the time of urethral catheterization after TURP.

Keywords: Transurethral Resection of the Prostate (TURP), Urethral Catheter, Benign Prostatic Hyperplasia.

Benign Prostat Hiperplazili Hastalarda Transüretral Prostat Rezeksiyonu Sonrası Erken Ve Geç Üretral Kateter Çekilmesinin Sonuçlarının Karşılaştırılması

ÖZET

Amaç: Prostatın transüretral rezeksiyonu (TURP), benign prostat hiperplazisine (BPH) bağlı alt üriner sistem semptomlarının cerrahi tedavisinde standart olarak kabul edilir. Ancak, üretral kateterin çıkarılma zamanlaması konusunda görüş birliği yoktur. Biz çalışmamızda TURP sonrası üretral kateterin erken veya geç çıkarılmasının uzun dönem etkilerini karşılaştırmayı amaçladık.

Gereç ve Yöntem: TURP uygulanan toplam 91 hasta prospektif olarak incelendi. Hastalar üretral kateterin erken (postop 1.-2. gün) ve geç (7. gün) çıkarıldığı iki gruba randomize edildi. Ameliyat sonrası 1, 3 ve 6. aylarda tüm hastalar tedavi başarısı açısından değerlendirildi. Ek olarak, uluslararası prostat semptom skoru (IPSS), yaşam kalitesi (QoL), maksimum akış hızı, işeme sonrası rezidüel idrar hacmi ve morbiditeler (hematüri, enfeksiyon, üretral darlık, tahriş edici semptomlar, yeniden ameliyat ihtiyacı) tüm ziyaretlerde sorgulandı.

Bulgular: Ameliyat sonrası dönemde her iki grupta ürodinamik çalışma, komplikasyonlar, IPSS ve QoL açısından istatistiksel fark saptanmadı. Sadece 3. ayda maksimum akım hızının erken grupta daha yüksek olduğu görüldü. Ancak her iki grupta da benzer sonuçlara rağmen, üretral darlıkların erken grupta gecikmiş gruba göre daha erken (sırasıyla 1 ve 3 ay) meydana geldiği görüldü.

Sonuç: TURP sonrası üretral kateterizasyon zamanı konusunda, görüş birliği olmayan bir konuyu aydınlatmaya çalıştık. TURP sonrası üretral kateterin erken veya geç çıkarıldığı gruplar arasında etkinlik ve komplikasyonlar açısından herhangi bir farkın ortaya çıkmadığı saptanmıştır. Ancak daha kesin bir sonuca varmak için uzun süreli ve geniş serili çalışmaların sonuçları beklenmelidir.

Anahtar Kelimeler: Transüretral Prostat Rezeksiyonu (TURP), Üretral Kateter, Benign Prostat Hiperplazisi.

INTRODUCTION

Benign prostatic hyperplasia (BPH) and prostatic obstruction associated with BPH are the most common cause of lower urinary tract symptoms (LUTS) in aging men. The probability of developing LUTS within 30 years due to BPH in asymptomatic men in their 40s is approximately 50% (1). Although there are many drugs and non-drug, non-surgical treatment options for relieving these symptoms, transurethral resection of the prostate (TURP) is the standard gold treatment and the most widely used and accepted method for patients need surgery. It is illustrated in large series of patients that TURP has a practical and permanent corrective effect on urodynamic parameters and clinic (2).

TURP has evolved tremendously over the past 20 years. Many technical improvements and growth of experience in endoscopic surgery have developed TURP over time to enable it to compete with other accepted minimally invasive methods. However, although it is the standard surgical technique, there is still no consensus about the time of catheter removal, and any guideline does not inform the duration of catheter use (3).

Urethral catheterization is a common practice for urinary drainage and irrigation in the early post-operative period. However, catheterization length shows significant differences between surgeons and centers. Expectations of the proponents of early removal of the urethral catheter are shorter hospital stays, earlier return to active life, and additional advantages such as lower morbidity. However, the literature on the effects of a long or short catheterization duration is still insufficient.

In this randomized prospective study, we aimed to compare the impact of treatment on the results in early (24 hours after control of bleeding) and delayed (5-7 days after control of bleeding) catheter removal groups in patients who underwent TURP in 6 months follow-up.

MATERIAL AND METHODS

We prospectively analyzed the data of 91 patients who underwent TURP for obstructive BPH in 2013. The ethics committee of our hospital approved our study (Ethical approval decision number 2013/403), we informed all patients about the complications of TURP, and we obtained informed consent.

TURP was performed using a standard technique with monopolar (26 F sheath; electrosurgical instrument system; Storz) and bipolar energy (Gyrus ACMI 26 F sheath) under spinal anesthesia. Surgical indications were medical treatment failure, recurrent urinary retention, recurrent and non-controlled UTI, bladder stone formation, and recurrent gross hematuria.

Patients were evaluated with a clinical history, digital rectal examination (DRE), prostate volume with abdominal ultrasonography, measurement of maximum flow rate and postvoid residual urine volume (PVR), urinalysis, urine culture, serum creatine and PSA level before the surgery. International Prostate Symptom Score (IPSS) and quality of life (QoL) questionnaires were also administered to the patients. A prostate needle biopsy was performed before the surgery for suspicious or abnormal DRE or PSA> 3 ng/ml to exclude patients with malignant histopathology.

Patients with prostate cancer, neurogenic disorders, urethral trauma, renal dysfunction, urethral stricture, and who had an endoscopic procedure before were excluded from the study.

Possible causes of voiding dysfunction were excluded with the pressure-flow study if patients under 50 years or with prostate volume <40ml.

During the operation, irrigation was provided with 5% mannitol for monopolar and isotonic solution for bipolar system. At the end of the operation, continuous irrigation was applied with a 22F 3-way Foley catheter using isotonic solution and continued until there was no hematuria. Antibiotic prophylaxis was used with 1g cefazolin preoperatively and 12 hours after the operation. In addition, patients were prescribed oral 500mg ciprofloxacin twice a day until two days after postoperatively catheter removal.

The patients were divided into two groups. Group I included 47 patients in whom catheters were removed 24 hours after control of bleeding, and Group II included 44 patients in whom catheters were removed seven days after control of bleeding.

In the early group, patients were discharged after catheter removal with two or three successfull voids. In the delayed group, patients were discharged with a urethral catheter and requested to come for catheter removal after seven days.

At 1, 3, and 6th months after the operation, maximum flow rate and residual urine volume were measured, and we questioned LUTS, IPSS, and quality of life during all visits. Additionally, all patients were examined for complications (bleeding, infection, urethral stricture, a necessity for re-operation, and the number of referrals to the clinic).

Statistical Analysis: The descriptive values of the data obtained in the study were organized in tables. It was examined with the Shapiro-Wilk test if numerical variables showed normal distribution. In addition, the Mann-Whitney test was used for numerical, chi-square test for categorical variables compared to early and delayed catheter removal groups. Also, the Friedman test was used to examine the periodic changes in the two groups separately. A P value <0.05 was considered statistically significant, and PASW (ver.18) program was used for calculations.

RESULTS

After TURP, 91 patients were randomized to early and delayed catheter removal groups; 47 and 44 patients were included, respectively. In terms of the energy source used during the operation, the monopolar resection rate was 19.1% in the early group; 25% in the delayed group and was not statistically significant. The mean duration of catheterization (±standard deviation) was calculated as 36±10 hours in the early group and 8±1 days in the delayed group. All patients were followed for at least 6 months. The baseline characteristics of the patients are presented in Table 1. There was no statistical significance between the values.

IPSS and quality of life were questioned in 1, 3 and 6th months; maximum flow rate and residual urine volume were measured; all patients were interviewed regarding complications during all visits.

During the follow-up period, voiding symptoms ceased in most of the patients. IPSS and QoL scores decreased to 7.4/1.8 and 6.1/1.5; Qmax increased from 8.2 to 16.5 and from 6.7 to 16.2 mL/s; in the first month, in early and delayed groups respectively.

Also, PVR was at an unmeasurable level in both groups (Table 2). The results in all visits were significantly different from preoperative data (P <0.05). No significant difference was detected in the two groups in the 1st month.

Table 1. Baseline characteristics of patients before TURP

	Early	**Delayed**
Characteristics	***Mean - SD***	
Number of patients	47	44
Age (y)	60±8	61 ± 10
Prostate volume (mL)	56 ±15	63± 12
Qmax (mL/s)	8.7±3.8	6.2±4.4
PVR (mL)	140	159
IPSS	21±4	21±4
QoL	4 ± 1	4 ± 1
PSA (ng/mL)	3.1±1.5	4.2±3.8

Qmax: maximum flow rate, PVR: post-voided residue volume, IPSS: International prostate symptom score, QoL: Quality of life, PSA: Prostate-specific antigen.

Table 2. Voiding variables after TURP

	Early group			**Delayed group**		
	1st month	*3rd month*	*6thmonth*	*1st month*	*3rd month*	*6thmonth*
			Mean±SD			
Qmax (mL/s)	16.5±7.8	18.3±6.1	19.7±5.7	16.2±7.2	14.9±5.8	19.3±6.7
PVR (mL)	17±44	6.1±15	6.4±16.6	2±4	4.1±8.5	5.1±10.7
IPSS	7.4±5.3	4.7±3.2	4.3±3.4	6.1±4.5	6.2±4.3	4.6±3.1
QoL	1.8±1.2	1.3±0.8	1.1±0.8	1.5±0.9	1.6±0.9	1.3±0.9

*Qmax: maximum flow rate, PVR: post-voided residue volume, IPSS: International prostate symptom score, QoL: Quality of life

In the 3th month, we found only the maximum flow rate (18.3 mL/s in early and 14.9 mL/s in delayed groups) significantly higher in the early group. Nevertheless, in the 6th month, there was no significant difference between the both groups regarding urodynamic parameters.

Post-operative evaluation; 3th month compared with the 6th month, differences for the IPSS and QoL were not significant between the two groups (p> 0.05). As the overview, up to 6 months, the IPSS and quality of life in both groups were in a constant decrease trend, and the flow rate was determined to increase continually.

In addition, the early and delayed groups were compared among themselves in terms of values measured at three different times after TURP. The maximum flow rates of post-operative month 6 were statistically higher than post-operative months 1 and 3 in the two groups. It was observed that IPSS decreased gradually at all visits in both groups. (Table 2).

The clinic admission frequency was assessed within 6 months after discharge to identify post-operative complications. In the early and delayed groups, the number of outpatient hospital admissions about urological symptoms was found to be 0.74 and 0.70, respectively; it was not statistically significant (p=0.870).

Patients were also questionnaired in all visits for dysuria, hematuria, urinary tract infection, and obstructive symptoms. Macroscopic hematuria was not observed in both groups after the removal of the urethral catheter. Only one patient received antibiotic treatment in the early group with the diagnosis of urinary tract infection. After urethral catheter removal, urinary retention occurred in one patient, and after the following four days, spontaneous voiding was seen in the early group. Dysuria continued up to 3 months in the early and delayed groups, 23.4%, and 22.7%, respectively. No differences were detected when all complications (dysuria, urinary retention, urinary tract infection) were compared in the two groups.

Five patients in each group required endoscopic procedures for urethral stricture or bladder neck stenosis during the 6-month follow-up period. In all five patients in the early group, urethral stricture was observed. The urethral

stricture occurred within 1 one month in 4 patients and 3rd month in one patient. In the delayed catheter removal group, two patients underwent endoscopy with urethral stricture, 2 had bladder neck stenosis, and one had meatal stenosis. Meatal stenosis developed within the first month after TURP. In the delayed group, we observed urethra and bladder neck stenosis three months after the removal of the catheter. The kind of stenosis and changes in development time in the two groups were not statistically significant ($p = 0.806$).

DISCUSSION

TURP is currently the gold standard surgical treatment for BPH-associated LUTS. Surgical techniques other than TURP are claimed to have more advantages in terms of complications. The necessity of urethral catheterization for bladder irrigation after TURP is accepted without question by all clinicians. However, there is no consensus on how long the catheter should be kept after the operation. Some recommendations about catheter removal time; 1-2 hours after surgery, surgical night, one day after surgery, or after 2-3 days (4,5,6). Nevertheless, the knowledge of the literature is not sufficient yet about how long the duration of catheterization must be and the long-term effects of catheterization.

When the studies carried out so far are examined, a randomized controlled prospective study investigating the long-term effects of early or delayed removal of the catheter has not been designed until today. Generally, the advantages of removing the urethral catheter in the early period (the first 24 hours after surgery) are suggested to shorten the hospital stay and reduce treatment costs (7). Mueller et al. reported that catheter removal on post-operative day 1 decreases hospitalization time from 3.1 to 1.2 days, providing advantages in terms of treatment costs (8). Indeed, the total length of stay in the hospital is an essential parameter in the total treatment costs. However, assuming no other morbidity and delayed catheter removal is planned, hospitalization is not mandatory after controlling bleeding. In our study, in which hospitalization times were similar in both groups, we think that we did not allow long-term catheterization to increase the cost of treatment.

After the operation, the development of urethral stricture causes includes large prostate, long operating time, the thickness of the urethral catheter, infected urine, and using a thick resectoscope (9). Our study showed no statistically significant difference between the two groups in prostate volume. Therefore, we can say no substantial difference in the duration of the operation. We tried to minimize the differences between variable values except for the catheterization time as much as possible.

It is a separate discussion on monopolar and bipolar systems using different technologies and irrigation solutions that have superiorities to each other in terms of efficacy and complications of TURP. Although the use of two different energy systems in surgery is considered the limiting factor of the study; since the usage rates of various systems in the two groups are similar, it can be accepted that the two methods applied have negligible effect on the results.

After TURP, the new mucosa will be created immediately on the bladder neck and membranous urethra in the operated area. In one study, it was reported that after the operation, blood clots, fibrin, and necrotic cells would be removed with urination and without urination for a long time; these accumulated cells can lead to a stricture (10). However, until now, this has not been proven as histopathologic or urodynamic. On the other hand cause of corrupted integrity of the mucosal surfaces during surgery due to contact with urine, inflammation, and scar tissue formation has been suggested to induce the development of urethral stricture (9). Nielsen et al.; reported that edema and progressive subepithelial inflammation occur due to urinary extravasation, and urinary passage into the mucosal barrier posed by increased intramural voiding pressure predisposes the formation of urethral stricture (11). Strictures of the prostatic urethra are related to delayed epithelialization and excessive fibrotic tissue growth (12). No significant differences were observed regarding the incidence of stricture in the two groups in our study. On the contrary, 4 of 5 strictures in the delayed group were observed in the 3rd month or later. This suggests that longer catheterization could only delay the urethral stricture. However, studies with larger groups are required to reveal this situation.

In a study with 64 patients, they removed the urethral catheter as soon as they had clear urine after TURP and discharged within 23 hours. During this period, none of the patients has voiding difficulty or re-catheterization due to clot retention not being required (13). In another study with 66 patients with the urethral catheter removed after TURP on 1, 2, and 3rd days, re-catheterized patients were evaluated. There was no statistically significant relationship between early urethral catheter removal and the development of urinary retention after TURP in this study with a limited number of patients (14). While urinary retention was observed in only one patient in the early group, it was not in any patient in the delayed group in our study.

Despite the efficiency and complication rates in many clinics and studies, there is a consensus that early removal of urethral catheters reduces costs. Our clinic's average urethral catheter removal time varies from 2 to 5 days after surgery. The duration of catheterization is not a strict rule but it is decided by the surgeon in charge. Regarding the duration of catheterization, the factors to be considered include resection time, prostate size, the duration of post-operative

bleeding, the patient's general medical status, and diseases that could interfere with bladder function (e.g. diabetes mellitus). In this study, patients in both groups with early and delayed catheter removal were discharged 2 or 3 days after the operation. The delayed group was released with a urethral catheter, then re-invited for removal. Thus, it was ensured that there was no significant difference between the two groups in terms of hospital expenses.

While determining the duration of catheterization after TURP, not only the physical characteristics of the patient but also their mental and psychological conditions should be taken into account. After TURP, patients may experience significant anxiety due to hematuria, urinary retention, irritative complaints, or urethral catheter, and their quality of life may deteriorate. Rarely, re-catheterization may be necessary. In a study in which urinary retention and the need for catheterization were significantly higher in the early group, patients stated that they would prefer to stay with a catheter for one more day after TURP (14). However, the early removal of the urethral catheter is thought to have many advantages; the presence of a catheter after the operation increases the quality of life of patients by preventing many post-operative complications in the early period may be considered. Our study shows that dysuria seen in the early period harms the quality of life in the early group. However, not statistically significant; complaints from dysuria in the delayed group were observed to be more slightly. Prospective controlled studies on this topic will provide objective data about urethral catheterization and quality of life.

On the other hand, some clinicians advocate for early removal of the urethral catheter; short-term urethral catheterization reduces the risk of urinary tract infection (15). However, in our study, a urinary tract infection was seen in 1 patient in the early group; it was not detected in the delayed group. Thus, the urethral catheter was left in place for a couple more days; it can be said that it did not cause a significant increase in the risk of infection.

CONCLUSION

We compared the six-months results of the two groups: early and delayed removal of urethral catheters. We think we have contributed to the literature on the subject that seems simple but essential. Our findings suggest that early or late removal of the urethral catheter after TURP does not play an important role in terms of surgical morbidity and the efficacy of treatment. However, long-term outcomes should be expected to reach a more definite conclusion, and randomized prospective studies with large series should be designed.

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RESEARCH ARTICLE

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The Crucial Role of Awareness and Education in Promoting Effective Diabetes Self-Management and Reducing the Risk of Complications

ABSTRACT

Objective: Disease awareness is a pivotal factor in the management of illness. In chronic and progressive conditions, such as diabetes mellitus (DM), this awareness can be as effective as pharmacological interventions. This study aimed to assess how aware diabetic patients are of the complications of their disease.

Methods: This cross-sectional survey included patients diagnosed with DM. A total of 14 survey questions, divided into 7 different categories, were directed at the patients. The singular questions evaluated the patients' awareness of the complications, while the associated-secondary questions aimed to inquire about the sources of their awareness.

Results: In this study, a survey was conducted with 300 diabetic patients, yielding a response rate of 90.2%. The mean age was 53.81 ± 9.87 years. The level of awareness of complications was high among all patients (80.5%). The awareness level of ocular-related complications was the highest, while that of neuropathy was the lowest (50%). When patients were categorized by educational status, education increased awareness but decreased adherence to combined drug use. The patients' doctors were identified as the most significant source of support for raising awareness of complications. This support was further enhanced by the educational level.

Conclusions: High levels of awareness of complications related to diabetes, still being primarily provided by doctors, and improvement of patients' educational status, can lead to a decrease in the number of patients with a poor prognosis. Therefore, increasing awareness of diabetes-related complications and improving patients' educational status may positively impact reducing the incidence of poor prognosis among diabetes patients.

Keywords: Diabetes Mellitus, Diabetic Complications, Disease Awareness.

Etkili Diyabet Öz-Yönetiminin Teşvik Edilmesinde ve Komplikasyon Riskinin Azaltılmasında Farkındalık ve Eğitimin Önemli Rolü

ÖZET

Amaç: Hastalık farkındalığı, hastalık yönetiminde önemli bir faktördür. Diyabet gibi kronik progresif bir hastalıkta bu bilinç ilaçlar kadar etkilidir. Bu çalışmada diyabetli hastaların hastalıklarının komplikasyonlarından ne kadar haberdar olduklarını değerlendirmek amaçlandı.

Gereç ve Yöntem: Bu anket çalışmasına diyabet tanısı olan hastalar dahil edilmiştir. Hastalara 7 farklı kategoride toplamda 14 anket sorusu yöneltilmiştir. Tekil sorular komplikasyonlardan haberdarlıklarını değerlendirirken, ilişkili-ikincil sorular ise haberdarlık kaynaklarını sorgulamakta idiler.

Bulgular: Üç yüz hastanın katıldığı çalışmada, cevap oranı %90.2 idi. Ortalama yaş 53.81 ± 9.87 idi. Tüm hastaların farkındalık düzeyi oldukça yüksekti (%80.5). Görme ile ilgili komplikasyonlarda farkındalık düzeyi en fazla iken nöropati ile ilgili olanlarda en düşük düzeyde idi (%50.0). Hastalar eğitim durumlarına göre kategorize edildiklerinde, eğitim durumu farkındalığı artırırken, kombine ilaç kullanımı uyumunu azaltıyor gibiydi. Hastaların komplikasyon bilinçlenmelerinde en yüksek yardımcı kaynak takip eden doktorları idi. Eğitim durumu ile bu destek daha da artmakta idi.

Sonuç: Diyabete bağlı komplikasyonların bilinçlilik düzeylerinin yüksek olması, bu bilincin halen doktorlar tarafından en üst düzeyde sağlanması ve hastaların öğrenim durumlarının iyileştirilmesi ile kötü prognozla seyreden hasta sayısını azaltacaktır. Bu nedenle, diyabetle ilişkili komplikasyonlar konusunda farkındalığın arttırılması ve hastaların eğitim durumunun iyileştirilmesi, diyabet hastalarında kötü prognoz insidansını azaltmada olumlu etki yapabilir.

Anahtar Kelimeler: Diyabet Mellitus, Diyabetik Komplikasyonlar, Hastalık Bilinci.

INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (1). DM is caused by a combination of genetic and environmental factors, including obesity and physical inactivity (1). According to the International Diabetes Federation (IDF), approximately 463 million adults were living with diabetes in 2019, and this number is expected to rise to 700 million by 2045 (2). This progress is attributed to factors such as population aging, urbanization, and unhealthy lifestyles. If left uncontrolled, DM can lead to a wide range of complications, including cardiovascular disease, neuropathy, retinopathy, and nephropathy, all of which can have a significant impact on the quality of life of those affected (3).

Diabetes is a major public health concern due to its high prevalence, associated complications, and economic burden (4). Although diabetes is a manageable condition, it requires ongoing medical care and patient self-management to prevent and manage complications. Given the serious consequences associated with DM, there is a pressing need to raise awareness about the condition. Early diagnosis and effective management of diabetes are crucial to preventing or delaying the onset of complications (5). This requires a comprehensive understanding of the risk factors, clinical presentation, and diagnostic criteria for DM, as well as knowledge of the various treatment options available (1, 6-8).

In this study, we conducted an analysis of the awareness levels and expectations of individuals who have been diagnosed with diabetes with regard to complications. The analysis was conducted through the use of a concise survey. By increasing awareness and knowledge of DM, we hope to empower individuals to make informed decisions regarding their health and well-being, and ultimately reduce the burden of this condition on individuals, families, and society as a whole.

MATERIAL AND METHODS

This survey-based and cross-sectional research was carried out with individuals who had received a diagnosis of diabetes and who sought medical attention at the Department of Internal Medicine of Necmettin Erbakan University Hospital. Prior to the study, approval was obtained from the Non-Drug Research Ethics Committee of the current university under consent number 2019/1972. In addition to the survey forms completed by all participants, informed consent forms were duly procured to ensure that the participants had been fully informed of the research objectives and had provided their voluntary consent to participate. The study recruited participants who were 18 years of age or older and had a prior diagnosis of diabetes or were newly diagnosed with the condition. Participants with comorbidities or secondary diabetic conditions were not discerned for the purposes of the study. The patients' demographic and clinical data, as well as their concurrent laboratory results, were retrieved from the digital hospital records. The type of medication used for diabetes and educational status were also noted.

The survey comprised a total of 14 questions, each of which was closely interrelated. The survey questions were designed to investigate different types of complications. The first two questions focused on ocular complications, questions three and four were aimed at assessing renal complications, questions five, six, nine, and ten were designed to explore cardiovascular complications, questions seven, eight, eleven, and twelve were intended to investigate neurological complications, and questions thirteen and fourteen were focused on acute complications. Patient survey responses were scored using a binary scale for single-digit questions and a five-point Likert scale for even-digit questions. In addition, odd-numbered questions were aimed at assessing the patients' level of awareness regarding complications. In contrast, even-numbered questions sought to ascertain the source of the knowledge in the event of a positive response to the former questions (Figure 1).

Statistical Analysis: The statistical analysis employed in this study utilized SPSS (version 26) to determine appropriate tests for comparisons based on the normality or skewness of the continuous data, with consideration given to sample sizes exceeding 30 in each group. Specifically, the independent t-test and one-way ANOVA were utilized for normally distributed data, while the Mann-Whitney U and Kruskal-Wallis tests were utilized for non-normally distributed data. In addition, Pearson correlation was employed for normally distributed data correlations, and Spearman correlation was utilized for non-normally distributed data correlations. Furthermore, the chi-square test was used for all categorical data comparisons. Reliability analysis of the survey responses was assessed by calculating Cronbach's alpha via the correlation matrix, with a reliability threshold of 0.7 or higher deemed acceptable (9). The appropriateness of the responses for exploratory factor analysis was evaluated using the KMO and Bartlett's tests. All analyses were deemed statistically significant at a threshold of $p < 0.05$.

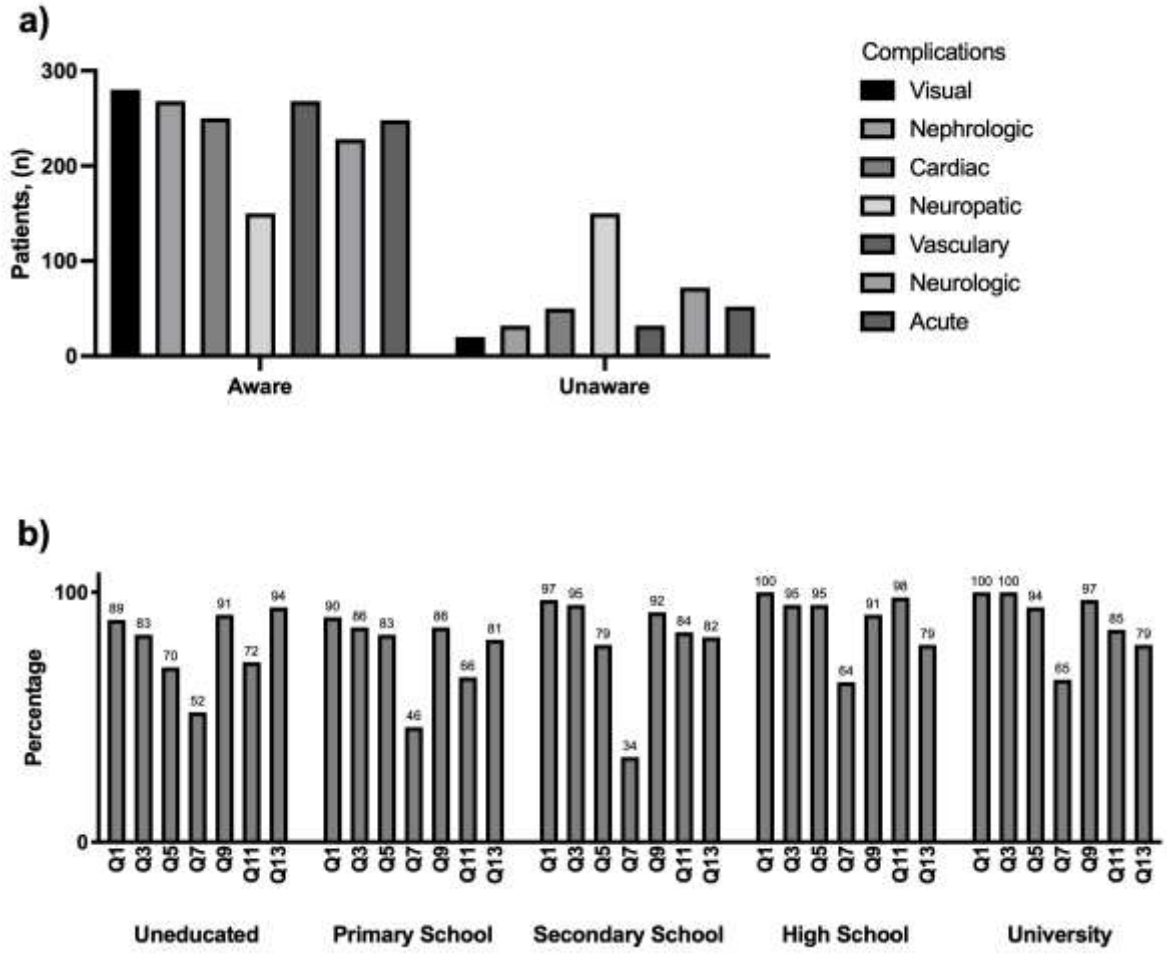

Figure 1. **a)** The awareness levels of all patients regarding diabetes-related complications; **b)** The distribution of complication awareness levels among patients based on their educational status.

RESULTS

In our study, we conducted a survey among a sample of 300 patients with DM and achieved a response rate of 91.2% and a completion rate of 90.2%. The mean age of the population was 53.81 ± 9.87 years and 166 of them were female (55.3%). The median age of onset of diabetes for all patients was 6 (3 - 12) years. Overall, 182 (60.7%) patients were using oral antidiabetic drugs (OAD), 78 (26.0%) were using insulin, and 40 (13.3%) were using both OAD and insulin in combination. The patients' clinical characteristics and laboratory values, classified based on their educational levels, are presented in Table 1.

The obtained Cronbach's alpha coefficient of 0.769 for the survey questions used in the reliability test indicates a moderate to a high level of internal consistency reliability. The overall awareness rates among the survey responses for complications were determined to be 80.5%. Upon evaluating the affirmative responses given to single-numbered questions that revealed the awareness of seven distinct complications, in accordance with the educational status of the participants, the following results were obtained: 78.6% for those who have not acquired literacy, 76.8% for primary school graduates, 80.5% for middle school graduates, 88.8% for high school graduates, and 88.6% for university graduates.

The survey responses indicate that patients demonstrated the highest awareness regarding complications associated with vision or blindness (93.3%) (Figure 1a). In contrast, the lowest level of awareness was observed for neuropathy-related complications (50%) (Figure 1a).

When the selectivity features of the survey questions were evaluated, it was observed that respondents who use both OAD and insulin, in question 9, exhibit a higher level of awareness compared to those who solely use OAD or insulin. Upon evaluating the selectivity of the questions with regards to educational status, it was observed that uneducated respondents displayed a higher level of awareness in providing "positive" responses to the first question, which pertained to visual complications (Figure 1b). Similar results were obtained in question 5, which inquired about cardiovascular complications (Figure 1b). In question 11, which inquired about neurological complications, individuals who completed primary school education could be considered more aware than other groups (Figure 1b).

Table 1. Clinical characteristics and prominent laboratory results of patients

Educational status	**Uneducated** (n = 46)	**Primary school** (n = 140)	**Secondary school** (n = 38)	**High school** (n = 42)	**Postgraduated** (n = 34)	*p* value
Age, year	60.72 ± 10.43	55.72 ± 8.52	52 ± 8.92	47.52 ± 7.68	46.38 ± 8.50	**0.001**
Gender, F / M, n (%)	34 (73.9) / 12 (26.1)	82 (58.6) / 58 (41.4)	23 (60.5) / 15 (39.5)	18 (42.9) / 24 (57.1)	9 (26.5) / 25 (73.5)	**0.001**
DM, year	10.5 (7 – 18.5)	7.5 (3.25 / 15)	5 (3 – 9.25)	3 (2 – 6)	2 (1 – 6.25)	**0.001**
DM treatment						
OAD, n (%)	19 (41.3)	76 (54.2)	23 (60.5)	36 (85.7)	28 (82.4)	**0.001**
Insulin, n (%)	13 (28.3)	46 (32.9)	12 (31.6)	2 (4.8)	5 (14.7)	**0.002**
OAD + Insulin, n (%)	14 (30.4)	18 (12.9)	3 (7.9)	4 (9.5)	1 (2.9)	**0.003**
Laboratory results						
Glucose, mg/dL	212.34 ± 45.39	209.92 ± 38.31	176.63 ± 45.12	189.85 ± 27.52	171.39 ± 46.72	0.067
HbA1c, %	8.61 ± 2.42	8.73 ± 1.92	8.17 ± 3.52	8.06 ± 1.57	7.93 ± 2.58	0.238
Creatinine, mg/dL	1.13 ± 0.27	1.12 ± 0.38	0.98 ± 0.47	0.97 ± 0.15	0.90 ± 0.25	0.173
Hemoglobin, g/dL	13.25 ± 0.28	13.73 ± 0.62	13.16 ± 0.59	13.82 ± 0.21	13.13 ± 0.53	0.538
TSH, mIU/L	3.34 ± 1.34	3.03 ± 1.92	3.29 ± 0.97	3.61 ± 1.84	3.49 ± 1.95	0.632
LDL, mg/dL	124.2 ± 33.5	132.5 ± 25.9	119.7 ± 39.5	116.6 ± 28.5	109.2 ± 23.8	**0.032**

The data are presented as mean and standard deviation or median and percentiles. The p-values were calculated using One-Way ANOVA and Chi-square test to compare all groups. **CAD**, Coronary artery disease; **CKD**, Chronic kidney disease; **DM**, Diabetes Mellitus; **F**, Female; **LDL**, Low-density lipoprotein; **M**, Male; **OAD**, Oral antidiabetic drug; **TSH**, Thyroid stimulating hormone.

The overall analysis of the responses regarding the source of awareness revealed that the highest source of knowledge was 47.5% from doctors, while the lowest was 2.7% from medical support teams (Figure 2a). The further representation of the sources of awareness according to educational status is presented in Figure 2b. Finally, the following logical correlations were identified. There was a positive correlation between age and diabetes duration ($p = 0.001$, $r = 0.534$), while education level was negatively ($p = 0.001$, $r = -0.461$) correlated.

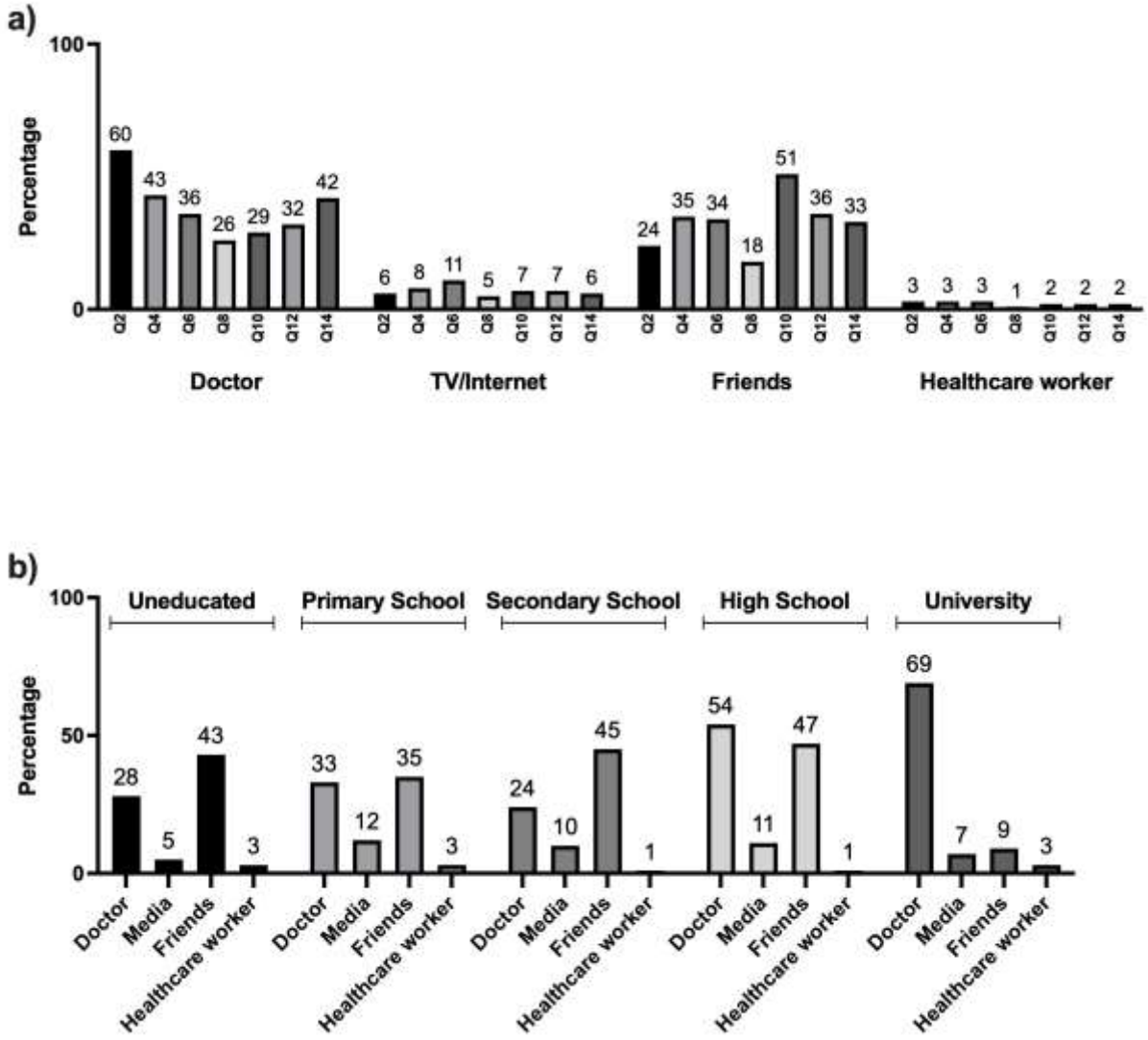

Figure 2. **a)** The sources of complication awareness among all patients; **b)** The components of complication awareness among patients based on their educational status.

DISCUSSION

The present study aimed to assess the level of awareness among diabetic patients regarding potential diabetes complications and the sources of this knowledge. The results revealed that the awareness level of diabetes complications was considerably high, and patients predominantly acquired this information from their attending physicians. Moreover, the education level was found to have a negative impact on the duration of diabetes, and its effect on awareness was pronounced. An intriguing observation was that insulin use decreased as the education level of the patients increased.

Awareness regarding one's illness is likely to exert a favorable influence on the progression of the patient's medical condition. Numerous studies have noted the significance of diabetes patients possessing knowledge about their illnesses. Diabetes patients must take charge of their health by engaging in regular exercise, consuming a nutritious diet, and correctly administering their medications. Additionally, it is crucial for patients to monitor their blood glucose levels independently. Extensive research has evidenced that blood glucose monitoring aids in preventing diabetes-related complications (10). Disease progression in diabetes is contingent upon several factors, such as lifestyle habits, control of blood glucose levels, and consistent medical check-ups. Nevertheless, it is widely acknowledged that patients who possess knowledge about their illness are better equipped to

regulate their blood glucose levels and forestall diabetes-related complications (11).

In our study, characterized by a noteworthy level of awareness regarding complications, it was observed that educational attainment exerted a positive influence on awareness. Nevertheless, it was also found that educational awareness had a bearing on resistance to the utilized or preferred treatment modalities. Specifically, in patients with lower educational levels, it was ascertained that insulin-based or adjunctive treatment options could be applied with greater ease. However, despite both educational awareness and medication options, it was noted that the average A1c levels of the patients did not reach optimal values.

Another crucial finding that can be inferred from the survey results is that patients' physicians who monitor their condition are their primary source of enlightenment. Close to half of all patients selected their physicians as their top choice for this source, while the second most common source was the Internet. This underscores the continued importance of doctor-patient collaboration in chronic diseases such as diabetes. Communication pertaining to diabetes persists not only within the domain of preventive measures but also during the phase of complications, contingent upon the priorities of either the healthcare provider or the patient (12). Notably, during the pandemic, a physician-based survey revealed delays in patient referrals despite 32% presenting with symptomatic manifestations (13).

As diabetes is known to increase the risk of vascular complications, including diabetic neuropathy, it is crucial for patients to have a high level of awareness and knowledge about these potential complications (14). This is especially important as diabetic neuropathy can be irreversible, and it can also pave the way for other vascular complications. Thus, it is imperative for patients to be well-informed about this condition and the steps they can take to prevent or manage it (15). The survey responses indicate that patients are still susceptible to complications in this context. Regardless of their educational level, patients exhibit low levels of awareness on this topic. Thus, patients should be trained in the best possible way regarding this knowledge gap.

Upon initial inspection, one of the most salient limitations of our study was the uneven distribution of participants across various patient subgroups. Notwithstanding the appreciable number of individuals with limited educational attainment, namely those who only completed primary school, this observation did not exert a confounding influence on the statistical computations. Additionally, we employed robust controls to account for potential covariates to bolster the credibility and generalizability of our findings. Moreover, the high response and completion rates indicate a strong engagement from the participants, enhancing our findings' validity. Using a sufficiently large sample size and rigorous methodology further increases the reliability of our study. As a final observation, the absence of inquiry into the participants' comorbidities would not only pertain to diabetes alone but also allow for assessing the awareness levels about other concomitant diseases.

CONCLUSION

Based on our study of the level of awareness among diabetic patients regarding complications, we have observed a higher level of awareness than expected. While education level had a positive impact on awareness, this was not the case for medication choice in diabetes treatment. Physician education still plays a more critical role in raising awareness compared to social media campaigns. High awareness of complications, which constitute an essential step in the mortality of diabetes, will contribute to improvements in disease progression.

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RESEARCH ARTICLE

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Evaluation of Antibiograms of *Escherichia coli* Strains Isolated from Urinary Cultures

ABSTRACT

Objective: Our aim in this study is to determine the antimicrobial resistance profiles of *Escherichia coli* strains known to cause urinary tract infections most frequently in the region, to obtain microbiological data about their current status, and to contribute to the development of clinical strategies for the prevention and management of these infections.

Methods: Our study includes patients with *E. coli* isolated from urine cultures. In the study, urine cultures and antibiograms of patients between January 2019 and January 2020 were scanned retrospectively. 662 patients over the age of 18 were included in the study. The files of the patients included in the study, the information registered in the system and the pre-filled forms were examined by examining age, gender, reproductive status in urine cultures, ESBL status, antibiograms, hospitalization status, admission outpatient clinic, reason for hospitalization, chronic and additional diseases, symptom status, the blood, nitrite, leukocyte parameters in the urinary dipstick test and the antibiotic treatment started were recorded.

Results: The antibiotics most frequently resistant to *E. coli* strains were cefuroxime (88.5%), tobramycin (75%), ceftazidime (72.9%), cefepime (59.5%) and ampicillin (57.5%). The antibiotics with the highest sensitivity were imipenem (100%), amikacin (99.1%), meropenem (98.2%), nitrofurantoin (96.3%) and fosfomycin (96.3%). It was observed that 25.7% of *E. coli* strains were ESBL positive.

Conclusions: Our findings showed that *E. coli* strains, which are the most common causative agents of urinary tract infections, have high resistance to many antibiotics commonly used in treatment. Considering the local resistance rates in empirical treatment and starting the treatment by making a urine culture will guide the treatment. As a result of our research, we think that the use of fosfomycin and nitrofurantoin in uncomplicated infections and the use of carbapenems and aminoglycoside antibiotics in complicated infections and upper urinary tract involvement are appropriate in the empirical treatment of urinary tract infections.

Keywords: *E. coli*, Urine culture, Urinary tract infection, Antimicrobial resistance.

İdrar Kültürlerinden İzole Edilen *Escherichia coli* Suşlarının Antibiyogramlarının Değerlendirilmesi

ÖZET

Amaç: Bu çalışmadaki amacımız idrar yolu enfeksiyonuna en sık neden olduğu bilinen *Escherichia coli* suşlarının bölgedeki antimikrobiyal direnç profillerini belirlemek ve güncel durumu hakkında mikrobiyolojik verileri elde etmek, bu enfeksiyonların önlenmesi ve yönetiminde klinik stratejiler geliştirilmesine katkıda bulunmaktır.

Gereç ve Yöntem: Çalışmamız idrar kültürlerinden *E. coli* izole edilen hastaları kapsamaktadır. Çalışmada 2019 ocak-2020 ocak tarihleri arasındaki hastaların idrar kültür ve antibiyogramları retrospektif olarak taranmıştır. On sekiz yaş üstü 662 hasta çalışmaya dahil edilmiştir. Hastaların dosyaları, sistemde kayıtlı olan bilgileri ve önceden doldurulmuş formları incelenerek yaş, cinsiyet, idrar kültürlerinde üreme durumu, GSBL durumu, antibiyogramları, hospitalizasyon durumu, başvuru polikliniği, yatan hastalarda yatış sebebi, kronik ve ek hastalıkları, semptom durumu, tam idrar tahlilindeki kan, nitrit, lökosit parametreleri ve başlanan antibiyotik tedavisi kaydedildi.

Bulgular: *E. coli* suşlarının en sık dirençli olduğu izlenen antibiyotikler sırasıyla sefuroksim (%88,5), tobramisin (%75), seftazidim (%72,9), sefepim (%59,5) ve ampisilin (%57,5) idi. Duyarlılığı en yüksek antibiyotikler ise sırasıyla imipenem (%100), amikasin (%99,1), meropenem (%98,2), nitrofurantoin (%96,3) ve fosfomisin (%96,3) idi. *E. coli* suşlarının %25,7'sinin GSBL pozitif olduğu görüldü.

Sonuç: Bulgularımız idrar yolu enfeksiyonunun en sık etkeni olan *E. coli* suşlarında tedavide sık kullanılan birçok antibiyotiğe yüksek direnç varlığını göstermiştir. Ampirik tedavide yerel direnç oranlarını dikkate alarak ve idrar kültürü yapılarak tedaviye başlanması tedavide yol gösterecektir. Araştırmamız sonucunda idrar yolu enfeksiyonunda ampirik tedavide komplike olmayan enfeksiyonlarda fosfomisin ve nitrofurantoin, komplike enfeksiyonlarda ve üst üriner sistem tutulumunda karbapenemler ve aminoglikozid grubu antibiyotiklerin kullanımının uygun olduğunu düşünmekteyiz.

Anahtar Kelimeler: *E. coli*, İdrar Kültürü, İdrar Yolu Enfeksiyonu, Antimikrobiyal Direnç.

INTRODUCTION

Urinary tract infections (UTI) are the most common bacterial infections encountered by physicians in all age groups (1). The annual global incidence of UTI is approximately 250 million and it is one of the most common medical problems in women (2, 3). It is stated that the second most common infection causing hospitalization after pneumonia is UTI (4).

UTI typically begins with periurethral contamination by an intestinal uropathogen, followed by colonization of the urethra and migration of the pathogen to the bladder, an event that requires extensions such as flagella and pili (5). In the bladder, it is determined whether uropathogens are successful in colonization or are eliminated as a result of complex host-pathogen interactions.

Infection by microorganisms differs according to reasons such as gender, age, duration of catheterization, underlying disease, faulty catheter care and lack of systemic antibiotic therapy (4, 6)

The most common cause of UTI is *Escherichia coli* from the Enterobacteriaceae family with a rate of 80-90% (1, 7, 8).

Classical diagnosis of UTI includes: taking history to identify recurrence experience and complicating factors, identification of symptoms including frequency, urgency and dysuria, physical examination of genitals and evaluation of suprapubic and flank pain, urinalysis using dipstick or microscopy and urine culture (9, 10). There are no leukocytes in the urine of healthy people, so the presence of leukocytes is considered an important criterion for the detection of pyuria. The test most closely related to culture on the dipstick was determined as the nitrite test (11). Urine culture is the gold standard test for the diagnosis of UTI (10,12).

UTIs are usually treated empirically with antibiotics as recommended by primary guidelines. Since the microbial spectrum of uncomplicated cystitis and pyelonephritis mainly consists of *E. coli*, local antimicrobial susceptibility patterns of *E. coli* should be considered in the empirical antimicrobial selection (13). Antibiotic resistance in *E. coli* strains isolated from UTIs is increasing day by day, making it an important public health problem, so it is very important to determine the antibiotic resistance patterns in *E. coli* isolates for correct prescriptions (14). *E. coli* infections that produce extended-spectrum beta-lactamase (ESBL) are particularly difficult to treat and increase morbidity, mortality, and treatment costs (15). ESBLs are beta-lactamases that can confer bacterial resistance to penicillins, first, second, and third generation cephalosporins and aztreonam by hydrolysis of these antibiotics (16, 17).

In this study, it was aimed to determine the antimicrobial resistance profiles of *E. coli* strains in the region, to obtain microbiological data about the current status, and to contribute to the development of clinical strategies for the prevention and management of these infections.

MATERIAL AND METHODS

This study includes patients with *E. coli* growth in their urine cultures who were studied at Erciyes University Medical Faculty Hospitals between January 2019 and January 2020. Urine cultures and antibiograms of the patients were scanned retrospectively.

The file numbers of the patients who could participate in the study were collected between the dates specified by the hospital information support unit, by searching for the word *'Escherichia coli'* in the urine culture results studied in patients over the age of 18.

A total of 662 specimens with a growth of 10^4 colony-forming units/ml and above in culture and for which antibiogram were studied were included in the study. Patients with *E. coli* growth in urine culture and patients over 18 years of age were included in the study.

This study was approved by the Erciyes University Clinical Research Ethics Committee's decision dated 09/09/2020 and numbered 2020/421, stating that there is no ethical objection to the study.

The files of the patients included in the study, the information registered in the system and the pre-filled forms were examined, and their age, gender, antibiograms, ESBL status, hospitalization status, admission outpatient clinic, reason for hospitalization, chronic and additional diseases (Chronic kidney failure , Diabetes Mellitus, hypertension, anemia, coronary artery disease, chronic obstructive pulmonary disease/asthma, malignancy, thyroid diseases, recurrent UTI, nephrolithiasis, kidney transplant, pregnancy, other), symptom status, the blood, nitrite, leukocyte parameters in the urinary dipstick test and antibiotic treatment started were recorded.

Statistical analyzes were performed using the SPSS version 15.0 (Chicago, USA) package program. The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogrov Smirnov, Shapiro-Wilk test). Descriptive statistics were expressed as mean and standard deviation in normally distributed numerical data, median and minimum-maximum values in non-normally distributed data, and numbers and percentages in nominal data. Normally distributed numerical variables were analyzed using the “independent groups t-test” between the two groups. Numerical variables that were not normally distributed were analyzed using the "Mann Whitney U test" between the two groups. Chi-square analysis and Fisher Exact test were used to compare nominal data. In the

statistical analyzes in the study, values below $p<0.05$ were considered statistically significant.

RESULTS

This study was completed with the inclusion of 662 patients over the age of 18 who had *Escherichia coli*-produced urine cultures and antibiograms in Erciyes University Medical Faculty Hospitals.

The mean age of the patients in the study was 57.7 ± 17.8 years. The mean age of male patients was 65.5 ± 15.0, and the mean age of female patients was 55.5 ± 17.9. Of the patients, 78.5% (n=520) were female and 21.5% (n=142) were male. The most frequent application place of the patients was found to be the emergency service (33.4%). The treatment method was outpatient treatment in 71.5% (n=473) and inpatient treatment in 28.5% (n=189) patients. In hospitalized patients, the reason for hospitalization was UTI in 69.5% (n=105) of the patients, while it was another reason in 30.5% (n=46). The most common comorbidities in the patients were chronic renal failure (44.7%), hypertension (40.6%), and Diabetes Mellitus (31%). While 71.8% (n=385) of the patients were symptomatic, 28.2% (n=151) were asymptomatic (Table 1).

Table 1. Sociodemographic and clinical characteristics of the patients

Feature		**Amount**
Age	Mean ± SD	57.7 ± 17.8
Gender	N (%)	
	Woman	520 (78.5)
	Men	142 (21.5)
Application Place	N (%)	
	Emergency service	221 (33.4)
	Nephrology	117 (17.7)
	Urology	77 (11.6)
	Infection diseases	77 (11.6)
	Gynecology and Obstetrics	24 (3.6)
	Rheumatology	23 (3.5)
	Endocrinology	21 (3.2)
	Physical therapy and rehabilitation	21 (3.2)
	Internal medicine	19 (2.9)
	Oncology	9 (1.4)
	Other[1]	30 (4.5)
Form of treatment	N (%)	
	outpatient	473 (71.5)
	inpatient	189 (28.5)
Reason for hospitalization	N (%)	
	UTI	105 (69.5)
	Other	46 (30.5)
Additional illness	N (%)	
	Chronic kidney failure	296 (44.7)
	Hypertension	269 (40.6)
	Diabetes Mellitus	205 (31.0)
	Anemia	177 (26.7)
	Coronary artery disease	107 (16.2)
	Chronic obstructive pulmonary disease/asthma	89 (13.4)
	Malignancy	82 (12.4)
	Thyroid diseases	78 (11.8)
	Recurrent UTI	46 (6.9)
	Nephrolithiasis	29 (4.4)
	Kidney transplant	20 (3.0)
	Pregnancy	7 (1.1)
	Other	272 (41.1)
Symptom	N (%)	
	Positive	385 (71.8)
	Negative	151 (28.2)

[1]*Other, cardiology (n=5), gastroenterology (n=4), dermatology (n=3), family medicine (n=3), orthopedics (n=3), neurology (n=3), hematology (n=2), general surgery (n=2), chest diseases (n=2), otolaryngology (n=1), pain outpatient clinic (n=1), neurosurgery (n=1).*

The antibiotics most commonly found to be resistant to *E. coli* strains in antibiograms were cefuroxime (88.5%), tobramycin (75%), ceftazidime (72.9%), cefepime (59.5%) and ampicillin (57.5%). The antibiotics with the highest sensitivity were imipenem (100%), amikacin (99.1%), meropenem (98.2%), nitrofurantoin (96.3%) and fosfomycin (96.3%) (Table 2).

Table 2. Antibiogram results and distribution of the patients

Antibiogram	**N**	**Sensitive**		**Resistant**	
		Number	**Percent**	**Number**	**Percent**
Ciprofloxacin	609	428	70.3	181	29.7
Trimethoprim-sulfamethoxazole	597	385	64.5	212	35.5
Nitrofurantoin	568	547	96.3	21	3.7
Gentamicin	511	422	82.6	89	17.4
Cefixime	473	333	70.4	140	29.6
Fosfomycin	465	448	96.3	17	3.7
Ceftriaxone	418	260	62.2	158	37.8
Ampicillin sulbactam	380	280	73.7	100	26.3
Ertapenem	237	228	96.2	9	3.8
Cefuroxime axetil	216	134	62.0	82	38.0
Amoxicillin-clavulanic acid	171	109	63.7	62	36.3
Piperacillin-Tazobactam	167	141	84.4	26	15.6
Amikacin	113	112	99.1	1	0.9
Ampicillin	80	34	42.5	46	57.5
Ceftazidime	70	19	27.1	51	72.9
Cefotaxime	67	41	61.2	26	38.8
Meropenem	57	56	98.2	1	1.8
Cefepime	37	15	40.5	22	59.5
Imipenem	36	36	100	0	0
Levofloxacin	36	19	52.8	17	47.2
Cefuroxime	26	3	11.5	23	88.5
Tobramycin	16	4	25	12	75
Other					
Cefazolin	8	1	12.5	7	87.5
Cefoxitin	4	2	50	2	50
Azithromycin	1	0	0	1	100
Netilmicin	1	0	0	1	100

It was observed that 25.7% of *E. coli* strains were ESBL positive. Patients were analyzed according to the presence of ESBL in *E. coli* strains. In ESBL-positive patients, the frequency of male gender was significantly higher than in ESBL-negative patients (p=0.001). The frequency of inpatient treatment in ESBL-positive patients was significantly higher than in ESBL-negative patients (p=0.002) (Table 3).

Table 3. The urinary dipstick test results of the patients

Feature		**Number**	**Percent**
The urinary dipstick test			
Leukocyte	*N (%)*		
	Positive	563	88.7
	Negative	72	11.3
Blood	*N (%)*		
	Positive	327	51.5
	Negative	308	48.5
Nitrite	*N (%)*		
	Negative	342	53.9
	Pozitive	292	46.1

In the urinary dipstick results of the patients, 88.7% (n=563) had leukocytes, 51.5% (n=327) blood, and 53.9% (n=342) nitrite (Table 4).

The most commonly preferred antibiotics in the treatment of UTI due to *E. coli* were cefixime (27.4%), fosfomycin (26.9%), ciprofloxacin (15.6%), and ceftriaxone (14.2%) (Table 5).

Demographic, clinical and laboratory results of the patients were analyzed according to their gender. The mean age of male patients was

significantly higher than female patients (p<0.001). The frequency of outpatient treatment was higher in female patients than in male patients (p<0.001). The presence of leukocytes (p=0.012) and blood (p<0.001) was observed more frequently in male patients in the urinary dipstick test. (Table 6).

Table 4. Treatments given to the patients and their distribution

Antibiotic	Number	Percent
Cefixime	156	27.4
Fosfomycin	178	26.9
Ciprofloxacin	89	15.6
Ceftriaxone	81	14.2
Ertapenem	75	13.2
Nitrofurantoin	46	8.1
Piperacillin-Tazobactam	28	4.9
Meropenem	15	2.6
Amoxicillin-clavulanic acid	14	2.5
Trimethoprim-sulfamethoxazole	4	0.7
Levofloxacin	3	0.5
Cefuroxime	3	0.5
Vancomycin	3	0.5
Ampicillin sulbactam	2	0.4
Imipenem	1	0.2

Table 5. Comparison of demographic, clinical and laboratory results of patients according to the presence of ESBL

Feature		ESBL (-)	ESBL (+)	*P*
Age	*Mean ± SD*	57.3 ± 18.3	58.6 ± 16.4	0.420†
Gender	*N (%)*			***0.001***††
	Women	402 (81.7)	118 (69.4)	
	Men	90 (18.3)	52 (30.6)	
Form of treatment	*N (%)*			***0.002***††
	outpatient	367 (74.6)	106 (62.4)	
	inpatient	125 (25.4)	64 (37.6)	
Reason for hospitalization	*N (%)*			0.311††
	UTI	64 (66.7)	41 (74.5)	
	Other	32 (33.3)	14 (25.5)	
Symptom	*N (%)*			0.489††
	Pozitive	282 (71.0)	103 (74.1)	
	Negative	115 (29.0)	36 (25.9)	
The urinary dipstick test				
Leukocyte	*N (%)*			0.718††
	Pozitive	419 (88.4)	144 (89.4)	
	Negative	55 (11.6)	17 (10.6)	
Blood	*N (%)*			0.703††
	Pozitive	242 (51.1)	85 (52.8)	
	Negative	232 (48.9)	76 (47.2)	
Nitrite	*N (%)*			0.833††
	Negative	254 (53.7)	88 (54.7)	
	Pozitive	219 (46.3)	73 (45.3)	
Treatment	*N (%)*			0.147††
	monotherapy	329 (79.1)	113 (73.4)	
	dual therapy	87 (20.9)	41 (26.6)	

†T test for independent groups, ††Chi-square test

Table 6. Comparison of demographic, clinical and laboratory results of patients by gender

Feature		Men	Women	*P*
Age	*Ort ± SS*	65.5 ± 15.0	55.5 ± 17.9	***<0.001***†
Form of treatment	*N (%)*			***<0.001***††
	outpatient	81 (57.0)	392 (75.4)	
	inpatient	61 (43.0)	128 (24.6)	
Reason for hospitalization	*N (%)*			0.269††
	UTI	37 (75.5)	68 (66.7)	
	Other	12 (24.5)	34 (33.3)	
Symptom	*N (%)*			0.243††
	Pozitive	92 (76.0)	293 (70.6)	
	Negative	29 (24.0)	122 (29.4)	
The urinary dipstick test				
Leukocyte	*N (%)*			***0.012***††
	Pozitive	127 (94.8)	436 (87.0)	
	Negative	7 (5.2)	65 (13.0)	
Blood	*N (%)*			***<0.001***††
	Pozitive	89 (66.4)	238 (47.5)	
	Negative	45 (33.6)	263 (52.5)	
Nitrite	*N (%)*			0.656††
	Negative	70 (52.2)	272 (54.4)	
	Pozitive	64 (47.8)	228 (45.6)	
Treatment	*N (%)*			0.522††
	monotherapy	98 (79.7)	344 (77.0)	
	dual therapy	25 (20.3)	103 (23.0)	
ESBL	*N (%)*			***0.001***††
	Negative	90 (63.4)	402 (77.3)	
	Pozitive	52 (36.6)	118 (22.7)	

†T test for independent groups, ††Chi-square test

DISCUSSION

UTI is the most common bacterial infection in the human population and is also one of the most common nosocomial infections (1). UTI treatment is often initiated empirically, and treatment is based on information determined from the antimicrobial resistance pattern of urinary pathogens (2). Antibiotic resistance in *E. coli* isolated from UTIs is increasing day by day and it is very important to determine antibiotic resistance patterns in *E. coli* isolates for correct prescriptions, since this makes it an important public health problem (18).

Since it is the most common pathogen in urinary tract infection, patients with *E. coli* growth in culture were included in our study. In many studies both in our country and in the world, *E. coli* was found to be the most common pathogen in urinary tract infections. (19, 20).

In the study of Teker et al. the mean age of men was found to be significantly higher (21). In a study investigating UTI in men, it was found that positive urine cultures increased with age (22). In our study, the mean age was found to be higher in men, which is consistent with the data.

In our study, the most resistant antibiotic was cefuroxime with a rate of 88.5%. Resistance rates in other cephalosporins vary between 72.9% and 29.6%. In the study of Yüksek et al. (23), 35% resistance to cefuroxime, 32% to cefotaxime, 26% to cefepime; In the study of Alanlı et al. resistance to cefuroxime 22%, cefixime 32%, and ceftriaxone 29% (24) was found. The activity of cephalosporins is significantly reduced in *E. coli* due to ESBL production. We think that cephalosporins are not a suitable option for the treatment of *E. coli* in UTI due to the high resistance rates detected. Even cefixime, a third-generation cephalosporin, was resistant to one-third of the strains in our study. The reason for such high resistance may be that it has a high gram (-) efficiency and is often prescribed in outpatients.

One of the most preferred antibiotics empirically in UTI is the quinolone group. In different studies conducted in our country, ciprofloxacin resistance was found to be 31.3% (83) in 2009, 24.8% (25) in 2014, and 41% (26) in 2019. In a study conducted with isolates collected from 2009 to 2011 in the United States of America, 25.8% resistance to ciprofloxacin was observed (27). If the rate of resistance to ciprofloxacin is below 10%, it is appropriate to choose empirically. (28). It is thought that there is an increase in the development of resistance due to the frequent use of ciprofloxacin in outpatient empirical therapy. In this study, ciprofloxacin resistance was found to be 29.7% and it was thought that it would be more appropriate to use according to the culture result in UTI.

In our study, trimethoprim-sulfamethoxazole resistance was found to be 35.5%. In different studies conducted in Turkey, the resistance rates

are; it varies between 34.9% and 57.5%. (19, 29, 30, 31). Resistance was found at a rate of 32.1% (27) in the USA and 47.3% (32) in Mexico. In the guidelines (28), it is recommended that trimethoprim-sulfamethoxazole should be the first choice for empirical treatment in cases where the rate of resistance does not exceed 20% in the treatment of UTI. When the resistance rates in our study and in our country are examined, it is thought that it should not be used in empirical treatment.

Its effectiveness with minimal drug resistance and side effects makes nitrofurantoin an attractive agent for cystitis (28). Nitrofurantoin resistance was found to be 3.7% in our study. In different studies conducted in our country in 2018 and 2019, nitrofurantoin resistance was found to be 4% (24, 26, 33). Our data were found to be compatible with other studies in our country. In a multicenter study, a sensitivity of 98.8% to nitrofurantoin was reported in *E. coli* isolates, and it is the recommended first-line therapy in national treatment guidelines (34). Nitrofurantoin shows that it can be preferred for empirical treatment in uncomplicated lower urinary tract infections due to low resistance.

Bayram et al. reported 5% (35) resistance, Aşgın et al. reported 4.1% (36) resistance, and Tekin et al. reported 2.2% (37) resistance for fosfomycin in our country.In the study of Naber et al. fosfomycin showed the highest sensitivity rate against *E. coli* with 98.1% (20). In our study, fosfomycin resistance was found to be 3.7%. Due to low resistance, it may be appropriate to use fosfomycin as first-line choice in the empirical treatment of *E. coli*.

In the guideline of the European Association of Urology, it is recommended to prescribe fosfomycin or nitrofuratoin as first-line treatment for uncomplicated cystitis, and not to use aminopenicillins and fluoroquinolones (38).

Aminoglycosides are often preferred in the treatment of serious infections caused by gram-negative bacteria (39). In our study, gentamicin resistance was found to be 17.4% and amikacin resistance was found to be 0.9%. In the study of Sağlam et al. (19) 19.3% resistance rates were found to gentamicin, and 7% in the study of Alanlı et al. (24).

Carbapenems are frequently used in the treatment of infections caused by ESBL-producing *E. coli*. In our study, imipenem was found to be the most sensitive antibiotic with 0% resistance. The ertapenem and meropenem resistances were found to be 3.8% and 1.8%, respectively. In different studies in our country, no resistance was found against imipenem and meropenem (19, 29). The high carbapenem sensitivities of the *E. coli* strains examined in our study can be interpreted as being related to their limited use and for certain indications.

According to the results of our research, it was concluded that while fosfomycin and nitrofurantoin are rational antibiotics that can be used in the treatment of lower urinary tract infections, carbapenems and aminoglycosides are alternatives that can be used in indications such as pyelonephritis and urosepsis. However, side effects such as ototoxicity and nephrotoxicity limit the use of aminoglycosides.

Today, morbidity-mortality and treatment costs are increasing due to the widespread use of antibiotics, especially the number of ESBL-producing strains and the developing antimicrobial resistance. In our study, *E. coli* strains were found to be ESBL positive in 25.7% of the patients. Durmaz et al. reported that ESBL production was 32.8% in a study conducted in 2015 (37). In the study conducted by Bayram et al. in 2010, ESBL production was found to be 29.9% (35). The ESBL rate in our study was found to be similar to the studies in the literature.

ESBL production was found to be significantly higher in male gender. The incidence of UTI in male gender increases with advancing age (40). With advanced age, an increase in prostate diseases, more hospitalizations and more exposure to antibiotics occur. This causes increased resistance, and this may be the reason for the high rate of resistant strains in males. In the study of Doğru et al. ESBL-producing *E. coli* strains were found to be higher in males, making a significant difference (41).

In our study, the most commonly preferred antibiotics in the treatment of UTI due to *E. coli* were cefixime (27.4%), fosfomycin (26.9%), and ciprofloxacin (15.6%). In a study investigating the antibiotic preferences of primary care physicians, quinolone group antibiotics, which were not primarily recommended in cystitis, were preferred most with 57% (42). The clinical picture in UTI is often simple cystitis (6), and in our study, it was seen that the majority of the outpatients were 71.5%. In this case, we can conclude that quinolones and third generation cephalosporins, which should not be preferred, are frequently used in our hospital. The reason for this may be that, since our study was conducted in a tertiary hospital, the possibility of infections caused by resistant and difficult-to-treat strains is high in most applications.

For rational antibiotic use, monitoring of regional and current resistance is of great importance in empirical treatment. Our study shows the current resistance rates in Erciyes University Medical Faculty Hospital in Kayseri province and that there is no similar study in this region in the literature. This is the strength of our work.

Due to the retrospective analysis of the data in our study, the inability to obtain information on the collection method of the studied urine samples is one of the limitations. Another limitation of our

study is that the study reflects the experience of a single center.

CONCLUSION

The most common organism in the etiology of UTI is *E. coli*. In our study, the data of patients with *E. coli* growth in 2019 in Erciyes University hospital in Kayseri province were examined.

We recommend the use of urine cultures, which is the gold standard for diagnosis, as it will prevent inappropriate antibiotic use and the development of resistant strains.

In our study, sensitivity was found to be high in fosfomycin, nitrofurantoin, aminoglycosides and carbapenems. As a result of these data, we recommend the use of fosfomycin and nitrofurantoin in uncomplicated and lower UTIs, carbapenems and aminoglycoside antibiotics in complicated and upper UTIs in empirical treatment.

Finally, our study's results may not be valid for areas with different epidemiological conditions. Therefore, we believe that the periodic determination of hospital antimicrobial resistance rates, and the selection of antibiotics according to antimicrobial sensitivity in the treatment of the agent will prevent the development of resistance.

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RESEARCH ARTICLE

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The Relationship of Hepcidin, Soluble Transferrin Receptor, Growth Differentiation Factor-15 And Anemia in Multipl Myeloma

ABSTRACT

Objective: Multiple myeloma (MM) is a malignant hematological disease and anemia is observed in the majority of patients. Hepcidin, Growth differentiation factor-15 (GDF-15), soluble transferrin receptor (sTfR) have been investigated in many forms of anemia, especially in chronic diseases and cancers. However, there are few studies investigating their role in MM. We aimed to determine the relationship between hepcidin, sTfR and GDF-15 levels in MM patients and their clinical features such as anemia parameters, disease stage and overall survival.
Methods: Hepcidin, sTfR and GDF-15 levels, as well as clinical and anemia-related parameters, were analyzed in newly diagnosed MM patients and healthy volunteers.
Results: Although MM patients had significantly lower Hb and Hct levels compared to the control group, none of the GDF-15, hepcidin and sTfR levels showed a significant difference between the groups. Among MM patients, we found that the anemic subgroup had significantly lower hepcidin levels than the non-anemic subgroup. GDF-15, hepcidin and sTfR levels showed weak or moderate, but statistically significant positive correlation with each other, while GDF15 was positively correlated with creatinine and sTfR levels were correlated with many parameters such as LDH, CRP, ferritin, albumin, creatinine, Hb and ISS, all of which weak. None of the levels of GDF-15, hepcidin and sTfR had a significant effect on survival.
Conclusions: We suggested that these mediators may play a role in anemia of MM but there is not a clear relashionship as in chronic disease anemia, there may be different mechanisms according to the characteristics of the patient groups.
Keywords: Multiple Myeloma, Anemia, Hepcidin, Growth Differentiation Factor-15 (GDF-15), Soluble Transferrin Receptor.

Multipl Miyelomda Hepsidin, Solubl Transferrin Reseptörü ve Büyüme Farklılaşma Faktörü-15'in Anemiyle İlişkisi

ÖZET

Amaç: Multipl myelom (MM) malign bir hematolojik hastalıktır ve hastaların çoğunluğunda anemi görülmektedir. Hepsidin, büyüme farklılaşma faktörü-15 (GDF-15), solubl transferrin reseptörü (sTfR) başta kronik hastalıklar ve kanserlerde olmak üzere birçok anemide çalışılmıştır ancak MM'daki anemide rollerini araştıran çalışmalar çok azdır. Multipl myelom hastalarında hepsidin, sTfR ve GDF-15 düzeylerini ve bu düzeylerin anemi parametreleri, hastalık evresi ve toplam sağkalım gibi klinik özelliklerle ilişkisini belirlemeyi amaçladık.
Gereç ve Yöntem: Yeni tanı almış MM hastalarında ve sağlıklı gönüllülerde hepsidin, sTfR ve GDF-15 düzeylerinin yanı sıra diğer klinik ve anemi ile ilişkili parametreler analiz edildi.
Bulgular: Miyelom hastaları kontrol grubuna göre belirgin düşük Hb ve Hct düzeylerine sahip olmalarına rağmen, GDF-15, hepsidin ve sTfR düzeylerinin hiçbiri gruplar arasında anlamlı bir farklılık göstermiyordu. MM hastaları içinde anemik alt grupta, anemik olmayan altgruba göre belirgin düşük hepsidin düzeyleri olduğunu saptadık. GDF-15, hepsidin ve sTfR düzeylerinin birbirleriyle zayıf ya orta düzeyde pozitif yönde korelasyon gösterirken, GDF15 kreatinin ile pozitif yönde köreleydi ve sTfR düzeyleri ise LDH, CRP, ferritin, albümin, kreatinin, Hb ve ISS evresi gibi birçok parametre ile ancak zayıf düzeyde korelasyon gösteriyordu. GDF-15, hepsidin ve sTfR düzeylerinin hiçbiri sağkalım üzerine anlamlı etkiye sahip değildi.
Sonuç: Bu mediyatörlerinin MM anemisinde bir rolü olabileceğini ancak kronik hastalık anemisindeki gibi net bir ilişki olmadığını, hasta gruplarının özelliklerine göre değişken mekanizmalar olabileceğini düşündürmüştür.
Anahtar Kelimeler: Multipl Myelom, Anemi, Hepsidin, Büyüme Farklılaşma Faktörü-15 (GDF-15), Solubl Transferrin Reseptör.

INTRODUCTION

Multiple myeloma (MM) is a malignant plasma cell disease which develops with a clonal increase of plasma cells in the bone marrow. The most important clinical findings defining the symptomatic disease are known as lytic lesions in the bones, deterioration in kidney functions, hypercalcemia and anemia. Anemia is present in 70% of patients at presentation and develops in 97% of patients during its course. (1) Anemia is usually normochromic, normocytic and its etiology includes invasion of bone marrow by tumor cells, inhibition of erythropoiesis due to tumor-microenvironment relationship, decrease in erythropoietin due to renal dysfunction, and inflammation-related factors. Some of the patients have iron deficiency and some have iron overload associated with the inability to use iron, and these iron metabolism disorders have been associated with organ damage and a decrease in overall survival (2). Although anemia in multiple myeloma is similar to anemia of chronic disease with many parameters, its mechanism has not been clarified.

Hepcidin is a circulating peptide hormone synthesized mainly from the liver and excreted in the urine, and is the main regulator of systemic iron balance (3). Hepcidin performs this regulation by coordinating the use and storage of iron, and by preventing the exit of iron to the plasma (3, 4). Recently, molecules from the transforming growth factor-β (TGF-β) family have been shown to be regulators of hepcidin. Growth differentiation factor-15 (GDF-15), also known as MIC-1, PLAB, PTGF-β, PDF or NAG-1, is a TGF-β family member whose production is induced in inflammatory or malignant diseases (5). GDF-15 downregulates the transcription of the HAMP gene encoding hepcidin in hepatic cell lines and downregulates hepcidin in vitro. The fact that increased GDF-15 levels are especially high in aggressive malignancies such as prostate, gastrointestinal, colorectal, and pancreatic cancers suggests that it also could have a role in cancer progression (6-9). Recent studies enounced that the severity of cancer-related anemia is related to GDF-15 levels and its interactions with hepcidin are important in the development of anemia in cancer (5). GDF-15 levels have been shown to be elevated in some anemia types characterized by ineffective erythropoiesis and iron overload, such as thalassemia, congenital dyserythropoietic anemia, and pyruvate kinase deficiency (10-12). On the other hand, another study, focused GDF-15 production in anemic states with different types of erythropoietic dysfunction reported that the hepcidin defect seen in this kind of anemia is associated with sTfR level, not GDF-15 levels (13).

Studies investigating this issue in patients with multiple myeloma are limited. Tarkun et al. reported that myeloma patients had significantly higher GDF-15 levels compared to controls and GDF-15 was correlated with some prognostic markers such as Beta-2 microglobulin and albumin, but could not clearly show its relationship with stage and survival (14). On the other hand, several studies reported elevated hepcidin levels in multiple myeloma (15, 16) but it is emphasized that hepcidin and GDF-15 levels will not be sufficient in erythropoiesis-related diseases, and sTfR measurements may provide clearer results (13). In the light of these studies, it can be thought that sTfR may give better results than hepcidin and GDF-15 in the evaluation of multifactorial anemia in MM disease. In this study, we aimed to measure hepcidin, sTfR and GDF-15 levels in multiple myeloma patients and to determine whether they differ from the control group and to determine their relationship with the depth of anemia, disease stage and known prognostic markers.

MATERIAL AND METHODS

This study was approved by Düzce University Faculty of Medicine Non-Invasive Ethics Committee with the decision dated 20.01.2015 and numbered 2015/110 and was supported by the Scientific Research Project of Düzce University BAP- 2015.04.03.336.

Patients who were newly diagnosed as multiple myeloma according to the diagnostic criteria of the International Myeloma Working Group and started to be followed up at our Internal Medicine and Hematology clinic were were evaluated for the study. Patients who were using drugs that can influence bone marrow or hematological parameters or transfused blood products in last 30 days were excluded from the study.

Considering similar studies in the literature (3,5,6), the sample size determination method and the total number of subjects to be used in the study, the effect size between control and MM group was calculated as 250 pg/ml. In order to determine that the 250-unit difference between the groups was statistically significant, the required minimum sample size was calculated as 26 in each group under the conditions of 90% power and 5% type I margin of error. Calculations were made with PASS v.11 package program. Basically, two groups (Multiple Myeloma and Control group) were compared in the study.

A total of 42 newly diagnosed multiple myeloma patients were evaluated, but the study was completed with 28 patients after the exclusions and with a control group consisted of 28 volunteers who did not have any complaints or disease. After 10 hours of fasting, blood samples were taken from the patient and control groups into empty tubes and immediately centrifuged. The obtained sera were stored frozen at -70°C throughout the patient collection process. After reaching the targeted number of patients and control groups, serum hepcidin, sTfR and GDF-15 levels were studied by

ELISA method (Huma Hepcidin 25 ELISA Kit, Human Soluble Transferrin Receptor1 ELISA Kit, Human Growth Differentiation Factor 15 ELISA Kit, FineTest®, Wuhan, respectively. Fine Biotech Co. Wuhan, China)

Routine tests performed in our hospital were evaluated for the diagnosis and staging of the patients. Urea, creatinine, total protein, albumin, calcium, C reactive protein (CRP), iron, total iron binding capacity (TIBC), ferritin, vitamin B12, folate and hemogram were analized on a daily basis, without delay.

Patients were subsequently grouped into anemic and non-anemic for secondary purposes according to their hemoglobin (Hb) values.

Statistical Evaluation: The distribution of the data was analyzed with the Shapiro-Wilks test, group comparisons were made with the Independent samples t-test for the continuous variables with normal distribution, and with the Mann-Whitney U test for the continuous variables that did not show normal distribution. Relationships between categorical variables were examined with Pearson chi-square or Fisher's Exact tests. Spearman correlation analysis was used to examine the correlation between continuous variables. Life tables and Kaplan-Meier survival analysis were used for survival analysis; groups were compared with Log-rank test. Statistical analyzes were made with the SPSS v.22 package program and the significance level was taken into account as 0.05.

RESULTS

The mean age of the 56 individuals included in the study was 65.70±9.22 (45-84) and there was no significant difference between patient and control groups (66.68±9.87 and 64.71±8.58, p=0.430). The overall male/female ratio was 23(41.1%)/33(58.9%) and were similar in both groups (p= 0.415).

Anemia parameters of both groups are detailed in Table 1. Revealing the anemia of the patient group, median Hb and hematocrit (Hct) levels were lower in the patient group (Hb 9.95 vs 13.40 g/dL and Hct 30.35% vs 40.00%, p<0.001). There were also statistically significant differences in mean corpuscular volume (MCV), red cell distribution width (RDW), platelet (Plt), TIBC, ferritin, vitamin B12 values, but the values were within normal limits. Ferritin was lower in the control group than in the patient group, but transferrin saturation (TS) was not different between the two groups (p=0.705).

Table 1. Hemogram and anemia parameters in patient and control groups

	Group	n	Mean ± SD	Median (min-max)	p
WBC (10^3/uL)	Patient	28	6030.36±2705.66	6100 (2000 - 14400)	0.121 #
	control	28	6700.00±1605.78	6800 (3500 - 9500)	
Hb (g/dL)	Patient	28	10.20±2.15	9.95 (6.70 - 14.49)	<0.001*
	control	28	13.49±1.47	13.40 (10.20 - 15.80)	
Hct (%)	Patient	28	31.00±6.68	30.35 (20.10 - 44.00)	<0.001*
	control	28	39.65±4.97	40.00 (29.10 - 48.00)	
MCV (FL)	Patient	28	90.01±7.52	90.35 (74.30 - 109.10)	0.045*
	control	28	86.23±6.23	86.40 (75.00 - 107.60)	
RDW (%)	Patient	28	17.29±3.94	16.60 (13.50 - 31.80)	0.011*
	control	28	15.06±2.08	14.45 (12.50 - 21.80)	
plt (10^3/uL)	Patient	28	217392.86±118759.74	190500 (50000 - 678000)	0.044 #
	control	28	244500.00±71796.78	234500 (133000 - 502000)	
Ferritin (ng/mL)	Patient	28	441.98±545.59	177.20 (3.87 - 1735.00)	<0.001 #
	control	20	46.89±44.24	41.10 (5.80 - 168.40)	
İron (µg/dL)	Patient	28	75.18±42.55	77.84 (14.00 - 202.00)	0.982*
	control	19	74.93±28.37	75.00 (25.60 - 123.00)	
TIBC (µg/dL)	Patient	28	279.34±61.54	284.50 (156.50 - 430.00)	<0.001*
	control	19	353.60±56.74	345.00 (240.80 - 462.00)	
TS (%)	Patient	28	28.54±18.74	27.91 (3.49 - 90.99)	0.135 #
	control	19	21.19±9.17	22.52 (5.14 - 37.76)	
B12 (pg/mL)	Patient	28	474.39±378.37		<0.001 #
	control	25	253.44±213.97	194.00 (30.00 - 1129.00)	
Folate (ng/mL)	Patient	28	11.70±7.93	8.11 (2.16 - 25.00)	0.671 #
	control	21	10.14±3.85	9.60 (5.12 - 23.40)	

*: Independent samples t test, #: Mann-Whitney U test

(WBC: White blood cell, Hb: Hemoglobin, Hct: hematocrit, MCV: mean corpuscular volume, RDW: red cell distribution width, Plt: platelet, MPV: mean platelet volume, PDW: platelet distribution width, TIBC: total iron binding capacity, TS: Transferrin saturation, B12: Vitamin B12)

Biochemical parameters, GDF-15, hepcidin, and sTfR levels in patient and control groups are given in Table 2. As expected, albumin levels were lower (median 3.50 g/dL vs. 4.24 g/dL, p<0.001) and sedimentation rate was higher (56 mm/hr vs. 18.5 mm/hr, p<0.001) in myeloma patients. Estimated glomerular filtration rate (eGFR) was lower and creatinine was higher in the patient group revealing impaired kidney functions. CRP, total protein, calcium, lactate dehydrogenase (LDH), GDF-15, hepcidin and sTfR levels were similar in both groups.

Table 2. Comparison of biochemical parameters, Growth differentiation factor-15, hepcidin and soluble transferrin receptor levels in patient and control groups

	Group	n	Mean ± SD	Median (min-max)	p
Sedim. (mm/h)	Patient	28	61.57±37.58	56.00 (4.00 - 140.00)	<0.001*
	control	12	24.67±19.92	18.50 (5.00 - 77.00)	
CRP (mg/dL)	Patient	27	1.40±2.53	0.64 (0.03 - 12.36)	0.540 #
	control	20	0.86±1.13	0.48 (0.15 - 4.66)	
T. protein (g/dL)	Patient	28	7.71±1.69	7.69 (4.08 - 11.15)	0.166*
	control	19	7.24±0.42	7.40 (6.50 - 7.84)	
Albumin (g/dL)	Patient	28	4.33±4.87	3.50 (1.82 - 29.00)	<0.001 #
	control	22	4.16±0.38	4.24 (3.20 - 4.61)	
Calcium (mg/dL)	Patient	28	9.78±2.00	9.38 (7.68 - 16.59)	0.653*
	control	26	9.60±0.55	9.55 (8.60 - 10.50)	
LDH (U/L)	Patient	28	233.21±131.71	192.00 (109.00 - 663.00)	0.083 #
	control	14	248.83±66.97	236.00 (156.00 - 371.60)	
Creatinine (mg/dL)	Patient	28	2.15±1.90	1.07 (0.47 - 6.51)	0.003 #
	control	28	0.80±0.21	0.81 (0.37 - 1.22)	
eGFR (mL/min/1.73m^2)	Patient	28	54.41±33.54	62.58 (6.88 - 102.90)	<0.001 #
	control	28	88.65±15.53	89.14 (52.50 - 116.80)	
GDF-15 (pg/mL)	Patient	28	1316.21±99.78	1288.20 (1209.74 - 1675.22)	0.057 #
	control	28	1270.39±43.16	1258.60 (1219.75 - 1378.46)	
Hep (pg/mL)	Patient	28	62053.39±7141.18	60697.58 (52382.24 - 77599.32)	0.207 #
	control	28	60489.33±8497.34	56728.30 (51234.98 - 86363.43)	
sTfR (ng/mL)	Patient	28	1230.02±89.10	1206.08 (1107.60 - 1382.03)	0.064 #
	control	28	1209.23±184.66	1178.65 (1112.96 - 2125.02)	

*: Independent samples t test, #: Mann-Whitney U test
(Sedim: Blood sedimentation rate, CRP: C reactive protein, LDH: lactate dehydrogenase, eGFR: estimated glomerular filtration rate, GDF-15: Growth differentiation factor-15, Hep: hepcidin, sTfR: soluble transferrin receptor)

There were 10 (35.7%) patients with stage I, 10 (35.7%) patients with stage II, and 8 patients (28.6%) with stage III according to International Staging System (ISS) and there was no significant difference in terms of GDF-15, hepcidin or sTfR levels between groups of stages. With Durie Salmon Staging, 13 patients were stage 1-2, 15 patients were stage 3A-3B, and there was no significant difference between these stage groups in terms of GDF-15, hepcidin or sTfR levels. The Karnovski score was >50 in 16 (57%) patients. There was no significant difference between low or high Karnovski score and GDF-15, hepcidin or sTfR levels (p>0.05). In order to investigate the differences between anemic and non-anemic myeloma patients, two groups were formed using the median Hb value (9.95 g/dL) in the patient group. As the details are summarized in Table 3, hepcidin level was lower in the anemic group (p=0.043), but there was no significant difference in GDF-15 or sTfR levels.

Table 3. Comparison of growth differentiation factor-15, hepcidin and soluble transferrin receptor levels in anemic and non-anemic patients

	Group	n	Mean ± SD	Median (min-max)	p
GDF-15 (pg/mL)	Hb<9.95 g/dL	14	1313.36±82.34	1296.79 (1221.60 - 1531.91)	0.783 #
	Hb>9.95 g/dL	14	1319.06±117.81	1278.63 (1209.74 - 1675.22)	
Hep (pg/mL)	Hb<9.95 g/dL	14	59157.46±5195.96	58139.87 (52382.24 - 72733.61)	**0.043** #
	Hb>9.95 g/dL	14	64949.32±7800.94	65507.04 (54121.11 - 77599.32)	
sTfR (ng/mL)	Hb<9.95 g/dL	14	1231.86±79.55	1206.08 (1132.60 - 1369.32)	0.662 #
	Hb>9.95 g/dL	14	1228.17±100.75	1205.33 (1107.60 - 1382.03)	

#: Mann-Whitney U test ; (GDF-15: Growth differentiation factor-15, Hep: hepcidin, sTfR: soluble transferrin receptor, Hb: Hemoglobin)

Transferrin saturation was calculated using the iron and total iron binding capacities of the patients. Patients with TS<10% (n=4) were classified as having iron deficiency. Although the group was very small, GDF-15, hepcidin and sTfR levels were not different from those with normal TS in patients with low TS. Similarly, in the analysis performed in the whole group, none of the Hb, ferritin, and TS values were significantly correlated with GDF-15, hepcidin and sTfR levels (Table 4).

Table 4. Investigation of correlations of hemoglobin, ferritin, transferrin saturation values with GDF-15, hepcidin and sTfR levels

		GDF-15	Hep	sTfR
Hemoglobin	r	0.075	0.295	-0.204
	p	0.705	0.127	0.299
Ferritin	r	-0.019	-0.131	0.328
	p	0.925	0.505	0.088
TS	r	-0.169	0.163	0.085
	p	0.391	0.407	0.666

(GDF-15: Growth differentiation factor-15, Hep: hepcidin 25, sTfR: soluble transferrin receptor, TS: Transferrin saturation)

When the correlations were examined, there was a positive moderate correlation between GDF-15 and sTfR (r=0.531, p<0.001) while both GDF-15 and hepcidin (r=0.303, p=0.023) and hepcidin and sTfR levels (r =0.286, p=0.033) showed significant but weak positive correlations. Additionally, GDF15 was positively correlated with creatinine (r=0.426, p=0.001), and sTfR levels were correlated with many parameters such as LDH, CRP, ferritin, albumin, creatinine, Hb and ISS stage, all of which weak. Correlation analyses are detailed in Table 5. When evaluated in terms of survival times, the mean overall survival rate (OS) in the anemic group was 26.2 ±4.5 months, the cumulative probability of survival was 0.786 ±0,110 for the 1st year and 0.524 ±0.168 for the 2nd year. The mean OS in the nonanemic group 44,7±10,8 months, and cumulative probability of survival was 0.67±0.14 both for 1st and 2nd years. Although the mean OS seems better in the non-anemic group, no statistically significant difference was found (p=0.703).

Using the median values of GDF-15, hepcidin and sTfR levels, patients were grouped and the effect of low or high values on survival was investigated. In the group with low GDF-15, mean OS was 34.5±7.9 and median OS was 55.4 months, while the cumulative probability of survival (CPS) at 1 and 2 years was 0.587, versus 45.9±12 .2 and 36.6±18.5 months with CPS rates of 0.836 and 0.597 in the group with high GDF-15. There was no statistically significant difference between the two groups (p=0.684). In the group with low hepcidin levels mOS: 53.3±14.3 months, mdOS:55.4±27.6 months, CPS was 0.762 for the 1st year and 0.653 for the 2nd year, not different from the patient group with high hepcidin levels (mOS: 31.8±7.05 mdOS:36.6±15.4 months, CPS 1st:0.665 and 2nd :0.554, p=0.345). Similarly, there was no statistically significant difference between OS time and CPS rates of groups of patients with low or high sTfR levels (mOS 53.57±14.1 months, mdOS 55.4±25.5 months, CPS 1st year:0.755, CPS 2nd year:0.647 in the group with low sTfR levels vs 32.5±7.2, 36.6±21.9, 0.675, and 0.563, respectively in the group with high sTfR levels, p=0.339).

Table 5. Investigation of the correlations of growth differentiation factor-15, hepcidin, soluble transferrin receptor levels with various clinical and laboratory parameters

		GDF-15	Hep	sTfR
Sedim.	r	-0.217	-0.283	-0.016
	p	0.268	0.144	0.936
CRP	r	0.324	0.160	0.388
	p	0.100	0.426	0.046
Hb	r	0.075	0.295	-0.306
	p	0.705	0.127	0.022
Hct	r	0.056	0.300	-0.204
	p	0.778	0.120	0.299
MCV	r	-0.306	-0.030	-0.069
	p	0.113	0.880	0.728
RDW	r	-0.127	-0.147	-0.085
	p	0.520	0.456	0.667
PLT	r	-0.025	-0.140	-0.287
	p	0.900	0.476	0.139
Ferritin	r	-0.019	-0.131	0.358
	p	0.925	0.505	0.012
İron	r	-0.141	0.111	0.088
	p	0.475	0.572	0.655
TIBC	r	0.008	-0.166	-0.151
	p	0.968	0.398	0.443
B12	r	-0.159	-0.014	0.093
	p	0.420	0.945	0.637
Folate	r	0.293	0.113	-0.073
	p	0.131	0.568	0.711
T. Protein	r	-0.324	-0.279	-0.400
	p	0.093	0.150	0.035
Albumin	r	-0.198	-0.175	-0.421
	p	0.314	0.374	0.026
Calcium	r	-0.077	-0.039	0.018
	p	0.696	0.844	0.928
LDH	r	0.125	0.177	0.467
	p	0.528	0.369	0.012
Creatinine	r	0.426	0.056	0.308
	p	0.001	0.778	0.021
eGFR	r	-0.408	-0.045	-0.355
	p	0.002	0.821	0.007
fLCR	r	-0.089	-0.369	-0.145
	p	0.695	0.091	0.521
GDF-15	r	1,000	0.303	0.531
	p	-	0.023	0,000
Hep	r	0.303	1,000	0.286
	p	0.023	-	0.033
sTfR	r	0.531	0.286	1,000
	p	0,000	0.033	-

(GDF-15: Growth differentiation factor-15, Hep: hepcidin, sTfR: Solubl transferrin receptor, Sedim: Blood sedimentation rate, Hb: Hemoglobin, Hct: hematocrit, MCV: mean corpuscular volume, RDW: red cell distribution width, Plt: platelet, MPV: mean platelet volume, PDW: platelet distribution width, TIBC: total iron binding capacity, LDH: lactate dehydrogenase, eGFR: estimated glomerular filtration rate, fLCR: free light chain ratio)

DISCUSSION

Multiple myeloma is a hematological malignancy that develops with clonal increase of plasma cells. Myeloma constitutes 1% of all malignancies and 10% of hematological malignancies. Although the data in our country are not conclusive, it is the second most common hematological malignancy in the United States (17, 18). While the incidence is 2/100,000, approximately 86,000 new cases are detected every

year around the world. Every year, 63,000 people die from MM, which corresponds to 0.9% of cancer deaths worldwide (19,20). It is a disease of the elderly population, as the average age of diagnosis is 69 years. Anemia is present in 70% of patients at presentation and develops in 97% of patients during its course (12). Anemia for the general population is defined by the World Health Organization as an Hb value below 12 g/dL in women and 13 g/dL in men, but the cut-off value for anemia in MM criteria is different and makes comparisons difficult. In order to compare the evaluations with the population, when Hb<12 g/dL anemia was accepted, anemia was found in 82% of our patients (23 of 28 patients) in our study. The median Hb value was 9.95 g/dl, which was below the level (Hb<10 g/dl) accepted by the International Myeloma Study Group as the criterion for symptomatic multiple myeloma. About half of the patients had anemia at the level indicated by the International Myeloma Working Group. In our stdy, when the admission symptoms were examined, it was found that the symptoms that caused the patient to consult a doctor were the symptoms of anemia in 32% of the patients, and MM was detected while investigating for anemia. When those with more than one symptom were taken into account, approximately 60% of the patients had symptoms of anemia.

Since anemia is a common condition in the elderly population, it is important to clarify the characteristics of multiple myeloma-associated anemia and to reveal the underlying mechanisms in the diagnosis and treatment of MM disease. In our study designed for this purpose, we closely examined the anemia parameters of MM patients. In addition to the fact that Hb and Hct were lower in the patient group (p<0.001), which clearly indicates anemia, MCV and RDW were also higher than in the control group. These findings were notable for the anemia of myeloma. While the median MCV was 90 fL in the patient group, it was similar to the median MCV 89.9 in the subgroup with anemia (p:0.388) and the MCV of only three patients was <80 fL. Therefore, patients generally had a normocytic anemia.

Vitamin B12 level was higher than the control group (mean 474.39±378.37 vs 253.44±213.97, p,<0.001) and therefore was not explanatory in terms of anemia. In the literature, there are studies reporting both low and high B12 levels in MM patients, and it is known that B12 level can be falsely measured in relation to paraproteins in the serum (21,22). The folate level was not different between the patients and the control group. Ferritin levels of the patients were significantly higher than the control group (median 177.20 vs 41.10 µg/L, p<0.001). Hypoferritinemia (<15 µg/L) was observed in only one non-anemic patient but hyperferritinemia was seen in 10 (35%) patients with higer values in anemic subgroup. Konig et al. reported 30% of patients with ferritin levels of 400-1000 µg/L and 24% of patients with >1000 levels much higher than our study (2), however, in this study, the patient group also included patients who received multiple treatments. On the other hand, Song et al. reported hyperferritinemia in 44% of their pre-treatment study population (23). Since ferritin is a well-known acute phase reactant, it is thought that it may reflect inflammation rather than iron stores, and transferrin saturation (TS) was examined in patients. Patients with TS<10% (n=4) were classified as having iron deficiency and although the group was very small, GDF-15, hepcidin and sTfR levels were not different in this group from those with normal TS. Similarly, Hb, ferritin, and TS values were not correlated with GDF-15, hepcidin and sTfR levels in the patient group. The number of patients with TS above 45% was only 2 (7%), much lower than that reported by Konig et al (22%). Since there was no significant difference in TS between the patient and control groups (p=0.135), it was thought that hyperferritinemia in the patients did not reflect iron overload.

Although myeloma patients had significantly lower Hb and Hct levels compared to the control group, none of the GDF-15, hepcidin and sTfR levels were significantly different between the MM and control groups. These findings were inconsistent with the study conducted by Tarkun et al. (14), which reported significantly higher GDF-15 levels in myeloma patients compared to controls. On the other hand, when the correlations of GDF15 were examined, except for its significant correlation with both hepcidin and sTfR, similar to the study of Tarkun et al., GDF15 had a positive correlation with serum creatinine level and therefore a negative correlation with eGFR. In our study, however, there was no significant correlation between hemoglobin, albumin, CRP or ISS or Durie Salmon Staging and GDF15. These differences may be due to the fact that both studies were conducted with relatively small groups, or they may be related to unpredictable conditions such as genetic risk factors that were not evaluated in both studies.

In our study, we found that hepcidin was not significantly different from the control group in MM patients, but it was significantly lower in the anemic subgroup among MM patients compared to the nonanemic subgroup. This was in contrast with previous studies suggesting that hepcidin elevation is one of the etiological causes of anemia in MM (15). When their correlations were examined, there was a moderate positive correlation with GDF15 and sTfR, but no correlation with parameters such as Hb, Hct, ferritin, creatinine, CRP or disease stage. It has been reported that hepcidin is increased in multiple myeloma in a few studies (15, 16, 24), but in the study of Haraguchi et al. (25), in which the prohepsidin measurement was used, there was no increase in prohepsidin levels in MM patients. In

that study (25), in the subgroup analyzes the prohepcidin levels were higher in patients with severe kidney damage than those with mild renal dysfunction and the control group. Similar to our results, Haraguchi et al also reported that there was no significant correlation between prohepcidin levels and other clinical parameters and anemia parameters including Hb. Sharma et al. (15) evaluated hepcidin expression in MM cells in their study, based on the high urinary hepcidin levels, and suggested that the increase in hepcidin did not originate from myeloma plasma cells, but rather that the increase in serum IL6 and other cytokines increased hepcidin production from hepatocytes. They reported that they did not see the same effect in the serum of each patient in the cell series they tested, and that no significant hepcidin production increase was observed in up to 30% of the patients. We think that the well-known heterogeneous character of the disease plays a role in whether this increase occurs or not. As Sharma et al. showed using anti-IL6 antibodies, hepcidin induction occurs by different mechanisms, with and without IL-6 dependent, and the contribution of these concomitant inflammatory mechanisms is likely to vary in selected patient groups. For example, although there was anemia level close to ours in the patient group studied by Sharma et al., all of the patients were ISS stage III patients. Hepcidin was not different from controls in a small number of MGUS patients included in the study. Therefore, in studies such as ours, in which patients with different ISS or Durie Salmon Stages are examined, consistent results may not be obtained due to the different mechanisms or levels of accompanying inflammatory processes. For example, in our study, CRP levels were not different from controls, suggesting that our patient group had lower inflammation levels, and there was no relationship between hepcidin and CRP.

In our study, sTfR levels were also not significantly different in MM patients from the control group, but they were positively correlated with many parameters such as GDF15, hepcidin, LDH, CRP, ferritin, albumin, creatinine, Hb and ISS stage, and negatively correlated with eGFR. The correlation between sTfR and GDF15 was strong, and since there are correlations to several clinical parameters, this parameter was thought to be particularly important for MM. The relationship between Hepcidin, sTfR, and GDF-15 was investigated in anemia associated with ineffective erythropoiesis, particularly in vitamin B12 deficiency anemia and thalassemia by Fertrin et al. (13). GDF-15 downregulates the HAMP gene encoding hepcidin, and an increase in GDF 15 may be a reason for the low hepcidin levels in patients with transfusion-related iron overload. In Fertrin's study, hepcidin and GDF15 were not correlated, and hepcidin levels were most strongly correlated with sTfR. These findings revealed that anemia in hematological diseases in which the erythropoietic system is affected in different ways cannot be explained only by the interaction of mediators originating from inflammation. Victor et al. investigated hepcidin and sTfR levels (24), but they found hepcidin levels to be high in the MM group and strongly negatively correlated with sTfR in their study. This may be due to the relatively small number of studies or the fact that Victor et al. worked with a younger patient group. Since there are not enough studies investigating sTfR levels for multiple myeloma, it is necessary to study with larger and more homogeneous groups with clinical information.

CONCLUSION

Although myeloma patients had significantly lower Hb and Hct levels compared to the control group, none of the GDF-15, hepcidin and sTfR levels were significantly different between the MM and control groups. We detected significantly lower hepcidin levels in the anemic subgroup among multiple myeloma patients compared to the nonanemic subgroup. When the correlations were examined, besides the significant correlations of GDF-15, hepcidin and sTfR levels with eachother, GDF15 was positively correlated with creatinine, and sTfR levels were correlated with many parameters such as LDH, CRP, ferritin, albumin, creatinine, Hb and ISS stage, all of which weak. None of the levels of GDF-15, hepcidin and sTfR had a significant effect on survival. These suggested that mediators of chronic inflammation may play a role in anemia in myeloma, but there is not always a clear interaction as in anemia of chronic disease, and there may be mechanisms involving partial response deficiencies and variable responses depending on the characteristics of patient groups. Since myeloma has a very heterogeneous structure, there is a need to continue studies by creating larger and clearer groups in terms of features such as genetic risk factors and clinical stages in order to explain these findings.

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RESEARCH ARTICLE

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Adapting to a New Normal: Changes in Behavioral Symptoms in Children with ADHD During Online Education

ABSTRACT

Objective: Children with neurodevelopmental disorders, such as Attention-Deficit Hyperactivity Disorder (ADHD), are considered a particularly vulnerable group due to the distress caused by the COVID-19 pandemic and associated social isolation measures. This study aimed to examine the alterations in symptoms of children with ADHD during the COVID-19 outbreak.

Methods: Sociodemographic data and ADHD symptom scores, measured using the Swanson, Nolan, and Pelham scale (SNAP-IV) parent form, were obtained from patient files from the same educational year prior to the pandemic. In addition to pandemic-related inquiries, parents were requested to complete the SNAP form again to assess their children's current conditions.

Results: Of the total 104 cases, 28.8% were female with a mean age of 10.5 (SD=2.4). There were no significant differences in ADHD symptom scores before and during quarantine. Participants who received regular online education had a significantly lower rate of externalizing problems. Children with parents who developed new onset negative emotional problems exhibited a significantly higher rate of internalizing problems. Participants whose fathers worked from home had a significantly lower rate of internalizing problems compared to children with fathers working in an office or who were unemployed.

Conclusions: The pandemic did not induce changes in the core symptoms of ADHD. It is inferred that educational planning for children, parental well-being, and accommodating parents' employment opportunities are among the most critical factors in maintaining the well-being of children and adolescents with ADHD during the pandemic period.

Keywords: ADHD, Covid-19, Online Education, Behavioral Symptoms, Children.

Yeni Normale Uyum Sağlamak: Çevrim-içi Eğitim Döneminde DEHB'li Çocukların Davranışsal Belirtilerindeki Değişimler

ÖZET

Amaç: Dikkat Eksikliği Hiperaktivite Bozukluğu (DEHB) gibi nörogelişimsel bozuklukları olan çocuklar, COVID-19 pandemisinin neden olduğu sıkıntılar ve ilişkili sosyal izolasyon önlemleri nedeniyle, özellikle hassas bir grup olarak kabul edilmektedir. Bu çalışmada, COVID-19 pandemisinde DEHB'li çocukların semptomlarındaki değişikliklerin incelemesi amaçlanmıştır.

Gereç ve Yöntem: Sosyodemografik veriler ve Swanson, Nolan ve Pelham ölçeği (SNAP-IV) ebeveyn formu kullanılarak ölçülen DEHB semptom skorları, pandemi öncesinde aynı eğitim yılındaki hasta dosyalarından elde edilmiştir. Pandemiyle ilgili sorulara ek olarak, ebeveynlerden çocuklarının mevcut durumlarını değerlendirmek için SNAP formunu tekrar doldurmaları istenmiştir.

Bulgular: Toplam 104 katılımcının yaş ortalaması 10.5 (SS=2.4) olup örneklemin %28.8'i kızlardan oluşmaktadır. Katılımcıların karantina öncesi ve sırasında DEHB semptom skorlarında anlamlı bir fark saptanmamıştır. Düzenli çevrim içi eğitim alan katılımcıların dışsallaştırma problemleri anlamlı derecede daha düşük bulunmuştur. Yeni başlangıçlı olumsuz duygusal problemler yaşayan ebeveynlere sahip çocuklarda içe yönelim sorunları anlamlı derecede daha yüksek oranda görülmüştür. Babaları evden çalışan katılımcıların içe yönelim sorunları, babaları ofiste çalışan veya işsiz olan çocuklara kıyasla anlamlı ölçüde daha düşük bulunmuştur.

Sonuç: Pandemi, katılımcıların temel DEHB semptomlarında belirgin değişikliğe yol açmamıştır. Pandemi döneminde DEHB'li çocuk ve ergenlerin esenlik halinin sürdürülmesinde eğitim planlamasının yanı sıra, ebeveynlerin esenlik düzeyinin ve istihdam olanaklarının en önemli faktörler arasında yer aldığı görülmektedir.

Anahtar Kelimeler: DEHB, Covid-19, Çevrim İçi Eğitim, Davranışsal Belirtiler, Çocuklar.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has presented an array of unprecedented challenges worldwide. While children appear relatively safe from severe illness, they are significantly impacted by the broader repercussions of the pandemic. Notably, children with neurodevelopmental disorders such as attention-deficit hyperactivity disorder (ADHD) constitute a particularly vulnerable group due to the distress precipitated by the pandemic and associated social isolation measures. ADHD is the most prevalent neurodevelopmental disorder in childhood, characterized by developmentally inappropriate symptoms of attention deficit and/or hyperactivity-impulsivity. It is reported to affect between 3% to 9% of children globally (1). ADHD often leads to behavior problems and social maladaptation (2). Children diagnosed with ADHD may struggle with low self-esteem and experience difficulties across various domains, including interpersonal relationships and academic performance (1, 3). ADHD is also associated with a diminished overall health-related quality of life and an increased risk for comorbidities in both children and adults (4, 5). The significance of ADHD treatment becomes more evident considering these potential outcomes. Treatment guidelines recommend pharmacological options, including stimulants & non-stimulants, as well as non-pharmacological psychosocial interventions such as behavioral therapy and school interventions (6, 7). Nevertheless, children with ADHD often face heightened challenges regarding academic and social achievement compared to their peers, underscoring their need for more structured environments (8).

The COVID-19 pandemic has profoundly altered daily life. In Turkey, schools closed early in the pandemic, and children were restricted from outdoor activities as a preventative measure. Educational activities have shifted to online platforms, disrupting traditional learning environments. Concurrently, parents have been working from home, adapting to new living conditions, and creating new routines, leading to evolving roles and boundaries within family structures. Children with ADHD are posited to be more susceptible to the distress caused by the outbreak and its consequences (9-11). Increased screen time and the lack of structured, face-to-face engagement offered in school environments could potentially exacerbate symptoms and precipitate emotional and behavioral changes in children with ADHD.

This study aims to investigate the behavioral symptoms of children with ADHD, believed to be influenced by significant changes in daily life, including quarantine and the shift to online education, during the COVID-19 outbreak. We hypothesize that ADHD symptoms would significantly worsen during quarantine, the frequency of new onset emotional and behavioral symptoms would increase compared to pre-pandemic assessments, and these changes would be associated with psychosocial factors during the pandemic.

MATERIAL AND METHODS

Our data collection took place from April 10th to 30th in 2020, during the online education period and curfew restrictions. We invited 150 parents of school-aged children with an ADHD diagnosis to participate in the study through phone calls, out of which 104 volunteered to participate. Parents provided online written informed consent, and measures were taken to ensure their anonymity. We collected sociodemographic data and ADHD behavioral symptom scores, which were measured using the Swanson, Nolan, and Pelham scale (SNAP-IV) parent form, from patient files from the same educational year before the pandemic. In addition to asking questions about the pandemic process, parents were asked to fill out the SNAP-IV scale to evaluate their children's current levels of inattentiveness and hyperactivity. The study received ethical approval from the Maltepe University Medical Faculty Ethics Committee (2021-90021).

Statistical Analysis: The data was analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 20. Descriptive statistics were presented as means with standard deviations or as frequencies (percentages). A 95% confidence interval was used for data interpretation. The chi-square test was employed to compare categorical variables such as gender, methylphenidate (MPH) usage, and internalizing and externalizing problems between groups. The independent sample t-test was utilized for evaluating continuous variables between two independent groups.

The paired sample t-test was used to compare the SNAP-IV Inattentiveness (IA) and SNAP-IV Hyperactivity/Impulsivity (H/I) scores from before and during the pandemic. One-way analysis of covariance was employed to adjust for socioeconomic status, MPH usage, and gender.

RESULTS

The analysis included 104 ADHD cases, of which 28.8% (n=30) were female, 71.2% (n=74) were male, and the average age was 10.5 (SD= 2.4, range: 6.3-15.0). Of the children, 53.8% (n=56) were in primary school, 41.3% (n=43) in secondary school, and 4.8% (n=5) in high school. 77.7% (n=80) of the mothers and 74.8% (n=77) of the fathers had university degrees.

During quarantine, 91.3% (n=95) of the children and adolescents with ADHD continued online education regularly, with an average daily duration of 3.4 (SD=1.7) hours. Of the sample, 69.2% (n=72) had regular reading times, 74% (n=77) participated in physical exercises regularly,

85.6% (n=89) were able to engage in outdoor activities, 92.3% (n=96) interacted online with relatives and friends, and 84.6% (n=88) played games with their families regularly.

In the same period, 34.6% (n=36) of mothers and 38.5% (n=40) of fathers started working from home, whereas 21.2% (n=22) of mothers and 52.9% (n=55) of fathers continued working at their offices. Meanwhile, 44.2% (n=46) of mothers and 8.7% (n=9) of fathers were unemployed, with 2.7% of fathers reporting job loss during quarantine. Only 1.8% of families reported COVID-19 infections, with no fatalities. In 69.2% (n=72) of the children, one or both parents reported negative emotional changes during the pandemic.

Average inattentiveness scores were 1.3 (SD=0.5) before quarantine and 1.2(SD=0.5) during quarantine, and mean hyperactivity scores were 1.1 (SD=0.7) before quarantine and 1.0 (SD=0.7) during quarantine. No significant differences were observed in inattentiveness and hyperactivity scores from before to during quarantine (p=0.094 and p=0.165, respectively). 57.7% (n=60) of the children were treated with MPH, and these children showed significant reductions in attention deficit and hyperactivity scores compared to children not on MPH (p=0.036 and p=0.047, respectively).

During the study, we adjusted for MPH use while evaluating whether ADHD symptoms differed from before to during quarantine based on the children's daily routines and parental negative emotional changes. We found no significant changes in inattentiveness and hyperactivity scores based on participation in regular online education, reading, physical activity, outdoor activities, playing with family members, and online interaction with friends and relatives. Likewise, parental negative emotional changes did not significantly affect ADHD symptom scores (Tables 1 and 2).

Table 1. Inattentiveness scores of children before and during quarantine

		Before		During Quarantine			
		Mean	SD	Mean	SD	F	*p*
Regular online education[a]	Yes	1.32	0.55	1.23	0.54	0.002	0.96
	No	1.52	0.76	1.44	0.69		
Reading books[a]	Yes	1.33	0.56	1.18	0.56	2.76	0.09
	No	1.34	0.58	1.41	0.53		
Regular physical activities[a,b]	Yes	1.32	0.60	1.22	0.57	0.074	0.78
	No	1.35	0.48	1.34	0.52		
Outdoor activities[a]	Yes	1.35	0.59	1.24	0.55	2.87	0.09
	No	1.20	0.40	1.34	0.59		
Online social interaction[a,c]	Yes	1.30	0.57	1.22	0.56	0.55	0.45
	No	1.65	0.39	1.63	0.35		
Family games[a]	Yes	1.33	0.56	1.24	0.53	0.06	0.80
	No	1.34	0.59	1.30	0.69		
Parental negative emotional changes[a]	Yes	1.40	0.55	1.16	0.54	1.03	0.36
	No	1.18	0.58	1.29	0.56		

[a]Adjusted for methylphenidate use, [b]Adjusted for gender, [c]Adjusted for socioeconomic status

Table 2. Hyperactivity scores of children before and during quarantine

		Initially		During Quarantine			
		Mean	SD	Mean	SD	F	*p*
Regular online education[a]	Yes	1.01	0.70	1.01	0.70	1.252	0.26
	No	1.50	1.00	1.50	1.00		
Reading books[a]	Yes	1.26	0.81	1.13	0.75	1.832	0.17
	No	0.87	0.58	0.89	0.67		
Regular physical activities[a,b]	Yes	1.25	0.79	1.13	0.77	0.503	0.48
	No	0.87	0.69	0.85	0.58		
Outdoor activities[a]	Yes	1.20	0.79	1.09	0.75	0.009	0.92
	No	0.87	0.61	0.81	0.56		
Social interaction[a,c]	Yes	1.02	0.72	1.02	0.72	0.616	0.43
	No	1.48	0.82	1.48	0.82		
Family games[a]	Yes	1.19	0.74	1.06	0.69	1.036	0.31
	No	0.94	0.92	1.02	0.96		
Parental negative emotional changes[a]	Yes	1.20	0.75	1.16	0.54	0.085	0.77
	No	1.03	0.82	1.29	0.56		

[a]Adjusted for methylphenidate use, [b]Adjusted for gender, [c]Adjusted for socioeconomic status

New onset internalizing problems, such as unhappiness and anxiety, were reported in 22.9% (n=24) of cases, while new onset externalizing problems, such as anger, were reported in 23.8% (n=24) of cases. Cases with regular online education had significantly fewer externalizing problems compared to those without. However, there was no significant relationship between other daily routines and internalizing or externalizing problems. Children whose parents had new onset negative emotional changes showed a significantly higher rate of internalizing problems. Cases where the father worked from home had significantly fewer internalizing problems compared to children with fathers working in an office or unemployed. Parental emotional and work status did not significantly relate to externalizing problems (Table 3).

Table 3. Presence of new internalizing and externalizing problems according to status of activity, parental mood and work during quarantine

		Internalizing			Externalizing		
		Yes N (%)	No N (%)	*p*	Yes N (%)	No N (%)	*p*
Regular online education[a]	Yes	21 (22.1)	74 (77.9)	0.421	20 (21.1)	75 (78.9)	0.035*
	No	3 (33.3)	6 (66.7)		5 (55.5)	4 (44.5)	
Reading books[a]	Yes	20 (27.8)	52 (72.7)	0.088	16 (22.2)	56 (77.8)	0.516
	No	4 (12.5)	28 (87.5)		9 (28.1)	23 (71.9)	
Regular physical activities[a,b]	Yes	19 (24.7)	58 (75.3)	0.514	16 (20.8)	61 (69.2)	0.189
	No	5 (18.5)	22 (81.5)		8 (33.3)	19 (66.7)	
Outdoor activities[a]	Yes	21(23.6)	68 (76.4)	0.76	22 (24.7)	67 (75.3)	0.692
	No	3 (20)	12 (80)		3 (20)	12 (80)	
Social interaction[a,c]	Yes	24(25)	72 (75)	0.193	22 (22.9)	74 (77.1)	0.395
	No	0 (0)	8 (100)		3 (37.5)	5 (62.5)	
Parental negative emotional changes[a]	Yes	21 (29.2)	51 (70.8)	0.023*	21 (29.2)	51 (70.8)	0.057
	No	3 (9.1)	30 (90.9)		4 (12.1)	29 (87.9)	
Paternal work status	Unemployed	3 (33.3)	6 (66.7)	0.007**	3 (33.3)	6 (66.7)	0.559
	At home	3 (7.5)	37 (92.5)		11 (27.5)	29 (72.5)	
	At office	18 (32.8)	37 (67.2)		11 (20)	44 (80)	
Maternal work status	Unemployed	9 (19.6)	37 (80.4)	0.417	11 (23.9)	35 (76.1)	0.271
	At home	4 (18.2)	18 (81.8)		4 (18.2)	18 (81.8)	
	At office	11 (30.6)	25 (69.4)		13 (26.9)	23 (73.1)	

[a]Adjusted for methylphenidate use, [b]Adjusted for gender, [c]Adjusted for socioeconomic status

DISCUSSION

Our study focused on assessing the impact of the COVID-19 pandemic and associated quarantine measures on children and adolescents diagnosed with ADHD. Our primary investigation centered around potential changes in ADHD symptom levels before and during quarantine, as well as the influence of new daily routines and parental emotional changes on these symptoms. The secondary aim was to explore the occurrence of new onset internalizing and externalizing symptoms during quarantine, and their correlation with daily routines and parental emotional and work status.

Our findings indicate that there were no significant differences in inattentiveness and hyperactivity scores before and during quarantine. We observed significantly lower symptom scores in children who were using MPH. Neither the new daily routines nor parental negative emotional changes influenced the change in ADHD symptoms after adjusting for MPH treatment use. This contrasts with a study from China that reported significant worsening in children's behavioral symptoms during the COVID-19 outbreak compared to their pre-pandemic state (12). In agreement with Bobo et al., we found inattention and hyperactivity levels to be similar to the pre-pandemic period (13).

The NIMH Multimodal Treatment Study of ADHD demonstrated that the combination of behavioral intervention and stimulant medication, as well as stimulant medication alone, were clinically and statistically superior to behavioral approaches. However, combination therapy did not have a significant advantage over stimulant therapy on core ADHD symptoms. Consistent with these findings, in our study, new daily routines and parental emotional changes neither enhanced nor reduced core ADHD symptoms (14).

As per the European ADHD Guideline Group, individuals with ADHD should, if clinically indicated, continue their pharmacological treatment during the COVID-19 pandemic (9). In our study, we discovered that approximately 20% of children and adolescents with ADHD developed new onset internalizing symptoms. A remarkably high proportion of parents experienced negative emotional changes due to the pandemic, with many caregivers reporting increased feelings of anxiety

and sadness for their children's emotional state. Interestingly, these parental negative emotional changes correlated with higher rates of internalizing problems in children and adolescents. This aligns with other studies that noted a correlation between children's and parents' negative mood states (12, 15, 16). Moreover, it's documented that the enforced social isolation during the pandemic increased the risk of depression and anxiety in the youth, underscoring the need for preventative support and early interventions catered to each country's needs and resources (17-20).

Contrarily, some studies found that most children and adolescents with ADHD either experienced stability or improvements in their well-being during the pandemic, with some reporting an alleviation in school-related anxiety according to parent reports (13, 21). In our own study, we found a correlation between fathers working from home and lower rates of new onset internalizing problems.

In addition to internalizing symptoms, we discovered new onset externalizing symptoms in approximately 20% of children and adolescents with ADHD. Interestingly, the prevalence of externalizing symptoms was lower in those who maintained regular online education during the pandemic. However, some other studies conducted during the pandemic reported that adolescents with ADHD had a decrease in routine adherence and encountered more difficulties with remote learning compared to those without ADHD (22). It was also found that parents of these children faced more challenges in supporting home learning (23).

Our study did present some limitations, including the reliance on parental reports due to COVID-19 restrictions that hindered direct evaluations of the children. Moreover, we did not use a standardized assessment scale to evaluate the presence of new emotional and behavioral symptoms, instead relying on questions directed to the parents. Despite these limitations, our study contributes some valuable insights into the effects of the COVID-19 pandemic on children and adolescents with ADHD. Importantly, our findings indicate that the pandemic has not significantly impacted the core symptoms of ADHD. However, internalizing and externalizing problems have been observed, suggesting the need for focused attention on these aspects. We highlight the importance of maintaining regular routines, such as online education, which seem to be associated with positive outcomes in terms of behavioral symptoms. Equally significant is the need to address parental well-being and job conditions, given their association with children's internalizing problems. These findings emphasize that maintaining the well-being of children and adolescents with ADHD during such challenging times requires a holistic approach, considering not just the child's routines and treatments, but also the broader family environment. Although the intensity of the COVID-19 pandemic has significantly waned, the learnings from this period remain vital, offering rich insights for future scenarios that might necessitate similar sweeping changes in lifestyle and societal functioning.

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

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RESEARCH ARTICLE

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Evaluation of Y Chromosome Microdeletion and Chromosome Analysis Results in Infertile Male Patients

ABSTRACT

Objective: Genetic testing for male infertility is rarely performed in our country. Male infertility is caused by chromosome number or structural problems, Y chromosome deletions and gene alterations. Infertility is a problem seen in 15% of couples. Genetic causes are responsible for the etiology of 3-10% of those diagnosed with male infertility due to oligozoospermia and azoospermia. In this retrospective study, we aimed to determine both the chromosomal structure and the microdeletion of the azoospermic factor (AZF) region on the Y chromosome in infertile men admitted to our center before the application of assisted reproductive techniques.

Methods: We studied 327 patients who applied to our laboratory for routine analysis. Chromosome analysis was performed from peripheral blood by conventional cytogenetic method. DNA was isolated from peripheral blood and Y chromosome microdeletion was analyzed by fragment analysis method with Y chromosome microdeletion detection kit.

Results: Out of 327 patients, 32 had cytogenetic and 18 had molecular abnormalities and 4 had both cytogenetic and molecular abnormalities. Numerical and structural anomalies were detected in patients with anomalous karyotype. Among the patients with Y microdeletions, 1 patient had AZFa, 2 patient had AZFb, 6 patients had AZFc, 3 patients had AZFc+d, 2 patients had AZFb+c+d, 1 patient had AZFb+c+sY160, 1 patient had AZFa+b+d+c+sY90, and 2 patient had AZFb+d+c+sY90.

Conclusions: Our study shows that chromosomal abnormalities and Y chromosome microdeletions are important causes of male infertility and that chromosome analysis and Y chromosome microdeletion tests should be performed to explain these abnormalities. It also emphasizes the importance of genetic counseling in explaining male infertility.

Keywords: Male Infertility, Chromosomal Abnormality, Y Chromosome Microdeletion.

İnfertil Erkek Hastalarda Y Kromozomu Mikrodelesyon ve Kromozom Analizi Sonuçlarının Değerlendirilmesi

ÖZET

Amaç: Ülkemizde erkek infertilitesi için genetik testler nadiren yapılmaktadır. Erkek infertilitesine kromozom sayısı veya yapısal sorunlar, Y kromozomu delesyonları ve gen değişiklikleri neden olmaktadır. İnfertilite çiftlerin %15'inde görülen bir problemdir. Oligozoospermi ve azoospermi kaynaklı erkek infertilitesi tanısı alanların %3-10'unun etiyolojisinde genetik nedenler sorumludur. Bu retrospektif çalışmada, merkezimize başvuran infertil erkeklerde yardımcı üreme teknikleri uygulanmadan önce hem kromozomal yapının belirlenmesi hem de Y kromozomu üzerindeki azoospermik faktör (AZF) bölgesinin mikrodelesyonunun belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Laboratuvarımıza rutin analizler için başvuran 327 hasta çalışıldı. Bu hastalardan konvansiyonel sitogenetik yöntemle periferik kandan kromozom analizi yapıldı. Periferik kandan DNA izolasyonu yapılarak Y kromozom mikrodelesyon belirleme kiti ile fragman analizi yöntemi ile Y kromozomu mikrodelesyonu araştırıldı.

Bulgular: 327 hastanın 32'sinde sitogenetik ve 18'inde moleküler, 4'ünde hem sitogenetik hem moleküler düzeyde anomali belirlendi. Anomalili karyotipe sahip hastalarda sayısal ve yapısal anomaliler saptandı. Y mikrodelesyon belirlenen hastaların 1'inde AZFa, 2 hastada AZFb, 6 hastada AZFc, 3 hastada AZFc+d, 2 hastada AZFb+c+d, 1 hastada AZFb+c+sY160, 1 hastada AZFa+b+d+c+sY90, 2 hastada AZFb+d+c+sY90 bölgelerinde mikrodelesyon saptandı.

Sonuç: Çalışmamız kromozom anomalilerinin ve Y kromozomu mikrodelesyonunun erkek infertilitesinin önemli bir nedeni olduğunu ve açıklanmasında kromozom analizi ve Y kromozomu mikrodelesyon testlerinin yapılmasının gerekliliği gösterilmektedir. Ayrıca, erkek kaynaklı infertilitenin açıklanmasında genetik danışmanlık vermenin önemini vurgulamaktadır.

Anahtar Kelimeler: Erkek İnfertilitesi, Kromozomal Anomali, Y Kromozom Mikrodelesyonu.

INTRODUCTION

Changes in chromosome structure and number can cause various conditions ranging from dysmorphic appearance to recurrent fetal loss and even infertility (1-11). Today, DNA sequencing platforms are quite advanced with the developing technology and can detect structural and point mutations in DNA structure. Genetic studies have revealed that in addition to structural changes, point mutations and small indels are effective in phenotype (12-14). Y chromosome microdeletion (YCM) is a genetic disorder in which part of the Y chromosome is missing. It causes male infertility by affecting the ability to produce sperm. YCM is the second most common genetic cause of male infertility after Klinefelter syndrome. The prevalence of YCM ranges from 3-10% in infertile men and is rarely seen in the population. Generally, it occurs in 10% of non-obstructive azoospermia, 7% of severe oligozoospermia, and 1-2% of mild to moderate oligozoospermia (15,16). It also differs between populations, being higher in those of African and Asian descent (17). Deletions can occur in any of the four regions of the Y chromosome, including AZF (azoospermia factor) regions a, b, c, and d. The exact cause of YCM is unknown, but it is thought to be caused by mutations that occur during meiosis or mitosis (18). The absence of one or more of the genes responsible for spermatogenesis leads to reduced or absent sperm production, resulting in male infertility. The severity of the phenotype varies depending on the size and location of the deletion. The most common clinical manifestation of YCM is male infertility, which may be azoospermia or oligozoospermia. Other clinical manifestations may include testicular atrophy, hypospadias, and increased risk of testicular germ cell tumors (19). The diagnosis of YCM is made by genetic testing, particularly Y chromosome microdeletion analysis. This analysis can detect deletions in any of the three AZF regions. The test is usually performed on a blood or semen sample. Micro-deletions are seen in the four subtypes of AZF, AZFa, AZFb, AZFc, and AZFd (20,21). The diagnosis of YCM has implications for genetic counseling and assisted reproductive technologies. There is no specific treatment for YCM, but assisted reproductive technologies (ART) can be used to achieve pregnancy in couples affected by YCM. Intracytoplasmic sperm injection (ICSI) is the most commonly used ART technique in men with YCM. In cases with azoospermia, assistive treatments are applied in reproduction by performing testicular sperm extraction (TESE) (22,23).

MATERIAL AND METHODS

Between 2020-2023, 327 infertile men who applied to Çam and Sakura City Hospital Genetic Diseases Evaluation Center were analyzed retrospectively. All studies were approved by the ethics committee of Basaksehir Cam and Sakura City Hospital in accordance with the standards of the Declaration of Helsinki, and written informed consent for medical examinations, genomic analyses were obtained from the patients (KAEK-2023.07.290). After obtaining genomic DNA samples, the screening of AZF deletions was performed by multiplex polymerase chain reaction (PCR) method using Genetek Biopharma GT-AZF Screen PCR kit (Genetek Biopharma GmbH, Berlin, Germany) in accordance with company protocols.

Y Chromosome Microdeletion: sY190, AZFa (sY86, sY265, sY84), AZFb (sY127, sY130, sY131), AZFd (sY152, sY153) and AZFc (sY254, sY255) regions on the Y chromosome and control regions (SRY, ZFX/ZFY, Y/ , AMXY,) is based on PCR amplification of sequence-labeled regions. PCR products were analyzed using the ABI PRISM 3500 DNA analyzer (Applied Biosystems, Foster City, CA, USA). Data analysis with GeneMapper v4.0 software (Applied Biosystems, Foster City, CA, USA).

Conventional Cytogenetics: For chromosome analysis, peripheral venous blood samples collected in heparinized tubes were inoculated into RPMI-1640 medium with phytohemagglutinin (PHA) and cultured at 37ºC for 72 hours. Colsemide was added 45 minutes before the study. Cultured blood cells were lysed with hypotonic solution and fixed with Carnoy's fixative. The cell suspension was spread on slides and aging was performed. The resulting chromosomes were analyzed after GTG banding in at least 20 metaphase plates.

RESULTS

Totaly 327 individuals who admitted to our Başakşehir Çam and Sakura Training and Research Hospital due to male infertility were included in the current study. The mean ages of individuals were 31.946±6.407 (min:16-max58). The distribution of the patients according to the indications is shown in Table 1. YCM was detected in 18 (5.5%) of 327 cases with primary male infertility and chromosomal abnormalities were detected in 32 (9.8%) cases (Table 2,3) (Figure 1).

Table 1. Indication distribution of patients.

Indication	Number	Percentage (%)
Azoospermia	204	62.4
Oligospermia	123	37.6
Total	327	100

Table 2. Y microdeletion results according to indication distribution of patients.

Indication	Azoospermia	Oligospermia
AZFa	1(0.5%)	0(0%)
AZFa + AZFb + AZFd + AZFc + sY90	1(0.5%)	0(0%)
AZFb + AZFc + AZFd	2(1%)	0(0%)
AZFb + AZFc + sY160	1(0.5%)	0(0%)
AZFb + AZFd + AZFc +sY90	2(1%)	0(0%)
AZFb	1(0.5%)	1(0.5%)
AZFc	3(1.5%)	3(2.4%)
AZFc + AZFd	1(0.5%)	2(1.6%)
NORMAL	192(94.1%)	117(95.5%)
Total	204(62.4%)	69(37.6%)

Table 3. Choromosomal abnormality results according to indication distribution of patients.

Karyotype	Azoospermia	Oligospermia
45,X[10]/46,XY[40]	1(0.5%)	0(0%)
45,X[48]/46,X,der(Y)[2]	1(0.5%)	0(0%)
45,XY,der(13;14)(q10;q10)	1(0.5%)	1(0.5%)
45,XY,der(15;22)(q10;q10)	1(0.5%)	0(0%)
46, XY, 22ps-	1(0.5%)	0(0%)
46,X,del(Y)(q11.23)	2(1%)	0(0%)
46,X,i(Y)(p10)	1(0.5%)	0(0%)
46,XY,inv(7)(p22q32)	1(0.5%)	0(0%)
46,XY,inv(9)(p11q13)	3(1.5%)	0(0%)
46,XYqh+	4(2%)	1(0.5%)
47,XXY	13(6.4%)	0(0%)
47,XYY	1(0.5%)	0(0%)
46,XY	174(85.3%)	121(99%)
Total	204(62.4%)	123(37.6%)

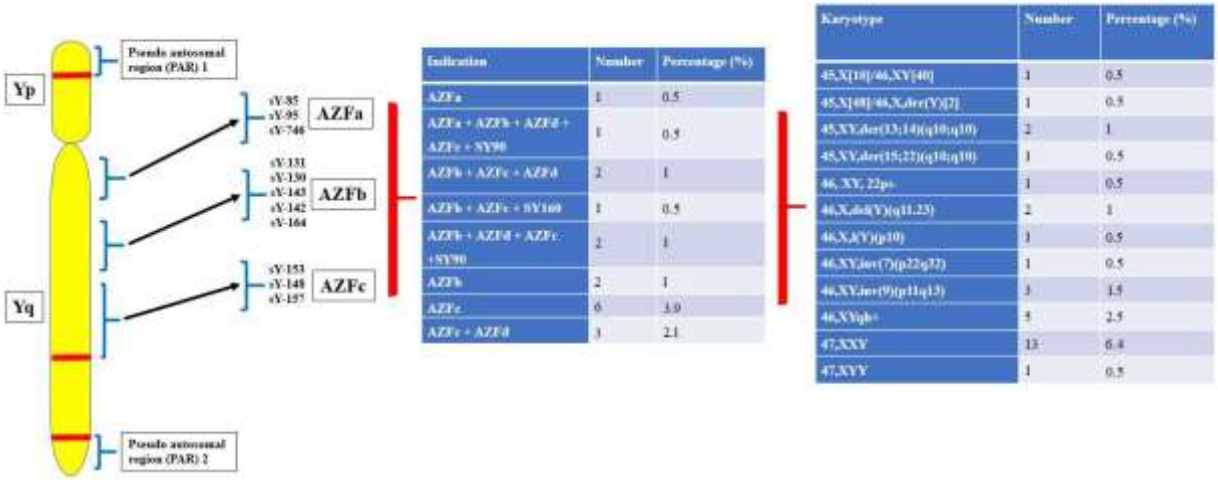

Figure 1. Y chromosome microdeletion test and distribution of chromosomal abnormalities in infertile patients.

The most common chromosomal abnormalities were found in the sex chromosomes (59.4%; 19/32). Others were autosomal translocations, additions or deletions of satellites (40.6%; 13/32). The most common chromosomal abnormality was Klinefelter syndrome (47,XXY) in 13 of 32 cases (Table 3) (Figure 1). Y microdeletion results according to indication distribution of patients were shown in the table 2. When the patients were divided as azoospermia and oligospermia, statistically significant differences were not found between two groups according to Chromosome Analysis results (χ2:17.321; p:0.138) (Table 3). When the patients were divided as azoospermia and oligospermia, statistically significant differences were not found between two groups according to Y microdeletion results (χ2:5.831; p:0.666) (Table 2).

In YCM, the AZFc region was found to be the most affected (33.3%), followed by AZF c+d (16.6%), AZFb+c+d (11.1%), AZFb+d+c+sY90 (11.1%), AZFb (11.1%), AZFa(5.5%),

AZFa+b+d+c+sY90 (5.5%), AZFb+c+sY160 (5.5%), respectively (Table 2). Abnormal karyotypes were found in 4 (22.2%) of 18 cases with YCM.

DISCUSSION

The male factor is responsible for 30-50% of infertility cases, and up to 20% of infertile men appear to be azoospermic (24). Azoospermia is generally observed with a frequency of 1% in the male population. Some conditions directly lead to azoospermia, while others occur after complex gene-environment interaction (24,25). A population-based study investigating the relationship between YCMs and male infertility showed that YCMs were significantly associated with infertility and azoospermia in this population (26-28). The prevalence of YCM varies between different populations, with some populations having a higher prevalence than others (29). Studies have shown that the prevalence of YCM is higher in infertile men, with rates ranging from 5% to 10% (30). The prevalence in the general population is estimated to be around 1 in 2000 men. The difference observed in these studies may be explained by the number of patients analyzed and the phenotype included in the studies. AZFc region deletions were most common in YCM and the Y chromosome contains several genes that play a role in male sex determination and fertility. YCM has been reported to cause loss of these genes, leading to various reproductive problems such as decreased sperm count, abnormal sperm morphology, and impaired sperm motility (31). However, some men with YCM may have normal sperm counts but still have difficulty conceiving due to other factors such as poor sperm motility or abnormal sperm morphology (32). In studies evaluating the efficacy of TESE and ICSI in men with FCM, it was found that TESE is a viable option for men with FCM and azoospermia, with an increased pregnancy rate. It was also emphasized that ICSI is effective in men with mild to moderate oligozoospermia (33,34). In a study, it was found that men with YCM who underwent IVF (in vitro fertilization) with ICSI had similar fertilization and pregnancy rates as men without YCM (35).

The most common type of YCM is the AZFc deletion, which occurs in the azoospermia factor c region of the Y chromosome (36) and the best prognosis is found in the AZFc deletion (37). MicroTESE is not recommended for complete AZFa, AZFb and AZFb+c deletions. The probability of finding sperm with micro-TESE in AZFc deletions is 50-60% (stahl2010). The transmission of AZFc region deletions to male babies is possible with the use of assisted reproduction method (38). However, some men with YCM have sperm production early in life and then have problems with sperm production. Therefore, it will be important steps for fertility of people with YCM or sex chromosomal abnormality to have their sons checked and, if necessary, to cryopreserve the sperm. However, pregnancy can also be achieved with the Preimplantation Genetic Diagnosis (PDG) method and options including the tran.

In our study, 327 infertile men were tested for YCM and CA. YCM was detected in 5.5% of patients, 9.8% of CA, and 1.2% of both YCM and CA (Table 2 and 3). While the frequency of chromosomal anomalies in the general population is approximately 0.6%-4%, it is reported as 2%-14% in male infertility cases (18). 5-15% of men with azoospermia or severe oligozoospermia have chromosomal abnormalities in an another study (7,39,40). In azoospermic men; The most common chromosomal abnormalities are Robertsonian translocations, inversions and Klinefelter syndrome (KS) (7,41,42). In our study, chromosomal variation was detected in 32 (9.8%) of 327 cases evaluated in terms of infertility. Except for the cases evaluated as chromosomal polymorphism, out of 23 (7%) patients, 14 numerical and 9 structural chromosomal variants were detected. 47,XXY (KS) was the most frequently detected chromosomal abnormality in our patient group (Table 3). CAs, whether numerical or structural, have serious adverse effects on fertility. CA was reported in 4% of patients who will undergo intracytoplasmic sperm injection (ICSI), 80% of which are related to the sex chromosomes (41,42) therefore, chromosomal analysis should be performed in patients evaluated for infertility.

KS is the most common genetic cause of male infertility and commonly affected individuals are taller than average and infertile. It is thought that the disease occurs as a result of the dosage effect of genes escaping from X inactivation in the extra X chromosome (43). In some cases, the symptoms are so mild that they are not diagnosed until puberty or adulthood. It is stated in the literature that 75% of the patients cannot be diagnosed in the early period (44). In our series, KS was found to be the most common chromosomal anomaly in infertility (13%), and we think that it is important to increase the awareness of clinicians in the early diagnosis of this disease. Patients with KS have small testicles that produce low amounts of testosterone. In some of the patients, sperm retrieval can be achieved by some specific methods called testicular sperm extraction; however because of the risk of gametes with chromosomal anomalies, these patients should be diagnosed with preimplantation genetics (45).

The relationship between YCM and testicular germ cell tumors has been investigated, and it has been reported that men with YCM have an increased risk of developing testicular germ cell tumors, especially those with partial or complete AZFc deletion (46). Although not fully established, it demonstrates that Y chromosome loss or ectopic expression of Y chromosome genes is closely

associated with a variety of male-based diseases, including selected somatic cancers (32,46).

Recent advances in genetic testing have allowed noninvasive detection of YCM using cell-free DNA in seminal plasma. This has the potential to reduce the need for invasive diagnostic procedures such as testicular biopsy (47,48). There is also ongoing research in the field of gene therapy for YCM, which may hold promise for future treatment options.

CONCLUSION

YCMs are a common genetic cause of male infertility. Diagnosis is made by genetic testing, and treatment options include assisted reproductive techniques such as ICSI and IVF. In our study, the genetic causes of male infertility who applied to our center were tried to be determinedThese genetic tests are the recommended test for all patients with azoospermia or severe oligospermia. Regenerative treatments such as stem cell therapy and gene therapy show promise in the treatment of male infertility caused by YCMs. These treatments aim to restore damaged or missing cells and genetic material to function properly to improve sperm production and function. Advances in genetic testing and regenerative therapies offer hope for the development of new treatments.

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RESEARCH ARTICLE

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Evaluation of Ultrasonographic Characteristics and Cytopathological Results of Autonomous (Toxic) Thyroid Nodules

ABSTRACT

Objective: Thyroid nodules are clinical conditions frequently encountered in the community and known to be associated with malignancy. In this study, it was aimed to determine the frequency of malignancy in patients diagnosed with autonomous (toxic) thyroid nodules (TTN). In addition, the effectiveness of ultrasonography (US) findings and fine needle aspiration (FNA) results in helping the diagnosis of malignancy were investigated.

Methods: Autonomous (Toxic) thyroid nodule was diagnosed by presence of nodule on US in the presence of subclinical or clinical hyperthyroidism, and detection of suppression in other parts of the gland with increased activity in scintigraphy performed with Tc-99m pertechnetate. Fine-needle aspiration was performed on patients who were considered suspicious by ultrasonographic findings. The histopathology results of the patients who were found to need surgical resection were recorded.

Results: 125 patients with autonomous (toxic) thyroid nodules were included in the study. Of the patients, 82 (65.60%) were female and 43 (34.40%) were male, with a mean age of 63.55±11.13 years. Ultrasonography revealed that nodules were less frequently located in the isthmus and left upper pole. The presence of microcalcification was detected in 8 (6.4%) patients. Histopathologically, the nodules of 2 (1.6%) patients were found to be malignant. Both patients who were found to be malignant were male and their nodules were seen as hypoechoic on US.

Conclusions: Since it has been seen that autonomic (toxic) thyroid nodules may be related to malignancy, careful evaluation of male patients with a hypoechoic image on US was considered appropriate.

Keywords: Toxic Thyroid Nodule, Malignancy, Ultrasonography.

Otonom (Toksik) Tiroid Nodüllerinin Ultrasonografik Özelliklerinin ve Sitopatolojik Sonuçlarının Degerlendirilmesi

ÖZET

Amaç: Tiroid nodülleri toplumda sık karşılaşılan ve maligniteyle ilişkili olduğu bilinen klinik durumlardır. Bu çalışmada otonom (toksik) tiroid nodülleri (TTN) tanısı konulan hastalardaki malignite sıklığını belirlemek amaçlandı. Ayrıca ultrasonografi (US) bulguları ve ince iğne aspirasyonu (İİA) sonuçlarının malignite tanısına yardımcı olmadaki etkinliği araştırıldı.

Gereç ve Yöntem: Otonom (Toksik) tiroid nodülü tanısı, subklinik veya klinik hipertiroidi varlığında US'de nodül ve Tc-99m perteknetat ile yapılan sintigrafide nodül veya nodüllere uyan alanlarda aktivite tutulumda artış ile birlikte bezin diğer kısımlarında supresyon saptanması ile kondu. Ultrasonografi bulguları ile şüpheli olarak değerlendirilen hastalara ince iğne aspirasyonu yapıldı. Cerrahi rezeksiyon gerekliliği saptanan hastaların histopatoloji sonuçları kaydedildi.

Bulgular: Çalışmaya otonom (toksik) tiroid nodülü saptanan 125 hasta dahil edilmiştir. Hastaların 82'si (%65,60) kadın, 43'ü (%34,40) erkek olup yaş ortalamaları 63,55±11,13 idi. Ultrasonografide nodüllerin isthmus ve sol üst polde daha az sıklıkla yerleştiği saptanmıştır. İzoekoik nodül görüntüsünün hipoekoik ve karışık eko görüntüden daha az olduğu görülmüştür (p<0,001). Mikrokalsifikasyon varlığı ise 8 (%6,4) hastada tespit edilmiştir. Histopatolojik olarak 2 (%1,6) hastanın nodülü malign olarak tespit edilmiştir. Malign olarak saptanan iki hasta da erkekti ve nodülleri US'de hipoekoik olarak görülmüştür.

Sonuç: Otonom (toksik) tiroid nodullerinin malignite ile ilgili olabileceği görüldüğünden, US'de hipoekoik görüntüsü olan erkek hastalarda dikkatli değerlendirme yapılmasının uygun olduğu düşünülmüştür.

Anahtar Kelimeler: Toksik Tiroid Nodulü, Malignite, Ultrasonografi.

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INTRODUCTION

Thyroid nodules are frequently encountered in the community. It is important in terms of affecting thyroid functions, mass effect and being associated with thyroid cancer at a rate of 7-15% (1). Autonomous (toxic) thyroid nodules (TTN) are formed by focal and/or diffuse hyperplasia of thyroid follicle cells and increased functional capacity, independent of the effect of thyroid stimulating hormone (TSH). With subclinical or clinical thyrotoxicosis, the presence of nodules is seen on physical examination or ultrasonography (US). Absence of thyroid antibodies and increased radioactivity uptake in the nodule or areas matching nodules on thyroid scintigraphy are used to detect TTN in order to differentiate it from other causes of thyrotoxicosis (2). Radioactive iodine (RAI) and thyroidectomy are applied as the definitive treatment method for TTN. The treatment method is preferred according to the patient's demographic and clinical characteristics, preference and the facilities of the health center (2).

The incidence of malignancy in TTN can range from 3% to 18.3% (3-6). The high rates detected show the importance of examining TTN in detail. Fine needle aspiration (FNA) is the gold standard method for differentiating benign and malignant thyroid nodules (2). In ultrasonography, hypoechoic appearance, solid structure, presence of microcalcification, contour irregularity, increased vascularity and increased strain index in elastsonography are suspicious findings in terms of malignancy (7,8).

In this study, it was aimed to determine the frequency of malignancy in patients diagnosed with TTN by physical examination, US and scintigraphy evaluations. In addition, the effectiveness of US findings and FNA results in helping the diagnosis of malignancy were investigated.

MATERIAL AND METHODS

Patients who applied to the Düzce Atatürk State Hospital Endocrinology and Metabolic Diseases outpatient clinic between June 2021 and December 2022 and were diagnosed with an autonomous (toxic) thyroid nodule were included in the study. Age, gender, TSH, fT3, fT4 values, ultrasound findings, cytology and histopathology results of the patients were saved.

Autonomous (toxic) thyroid nodule was diagnosed by presence of nodule on US in the presence of subclinical or clinical hyperthyroidism, detection of increased activity uptake in the nodules and suppression in other parts of the gland in scintigraphy performed with Tc-99m pertechnetate.After providing euthyroidism with beta-blocker and/or antithyroid treatment, FNA was performed on the indicated nodules.

Preoperative US and FNA procedures were performed using Siemens Medical Solution brand and MCMD01AA model USG device (Italy). Nodule volume, increased anterior-posterior diameter, contour irregularity, echogenicity, presence of microcalcification, thyroid pole where the nodule is located, and nodule dimensions were determined by US. The volumetric assessment of the thyroid nodule was calculated based on the use of the ellipsoid model. In this model, the height, width and depth of each nodule were measured and multiplied, and the result was then multiplied by the mathematical constant or correction factor (0.524) to calculate the volume of the nodules (9,10).

Fine-needle aspiration was performed on patients who were considered suspicious by US findings. For FNA, 10 ml injectors with 27 gauge needles were used. FNABs were performed with the patient in the supine position without the use of anesthesia. In the supine position, the neck was extended and the area to be biopsied was cleaned with 10% povidone-iodide. FNAB was performed under US guidance. Liquid-based cytology technique was used. The cytology results of the FNA samples evaluated in the pathology laboratory of our hospital were grouped as benign, malignant and atypia of uncertain significance according to the Bethesda classification. The histopathology results of the patients who were found to need surgical resection were recorded.

The study was approved by the local Clinical Research Ethics Committee with the decision dated 28.07.2023 and numbered 242.

Statistical Analysis: IBM SPSS 23.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago, USA) statistical package program was used for the statistical evaluation of the research data. Categorical data were summarized as frequency and percentage. Chi-square Test, Fisher's Exact and Fisher-Freeman-Halton Tests were used to evaluate the statistical difference of categorical data. p value of <0.05 was considered statistically significant.

RESULTS

125 patients with autonomous (toxic) thyroid nodules were included in the study. Of the patients, 82 (65.60%) were female and 43 (34.40%) were male, with a mean age of 63.55±11.13 years. Histopathologically, the nodules of 2 (1.6%) patients were found to be malignant. Ultrasonography revealed that nodules were less frequently located in the isthmus and left upper pole. It was observed that the isoechoic nodule image was less than the hypoechoic and mixed echo image ($p<0.001$). The presence of microcalcification was detected in 8 (6.4%) patients. A total of 78 (62.4%) patients underwent FNA. One of the two patients who were evaluated

as malignant as a result of FNA was also found to be malignant histopathologically. The laboratory, US, FNA and histopathology results of the patients are shown in Table 1.

Table 1. The laboratory, US, FNA and histopathology results of the patients

Laboratory results	Mean±SD		
TSH (n=121)	0.075±0.082		
fT3 (n=88	3.456±0.935		
fT4 (n=113)	2.129±10.431		
Nodule volume.	10.423±16.512		
US results			p
Nodule site	n	%	
Right upper pole	13	10.4	<0.001
Right middle pole	25	20.0	
Right lower pole	30	24.0	
Left upper pole	**7**	**5.6**	
Left middle pole	22	17.6	
Left lower pole	24	19.2	
Isthmus	**4**	**3.2**	
Nodule	n	%	
Mixed echo	62	49.6	**0.049**
Hypoechoic	50	40.0	
Isoechoic	**13**	**10.4**	
Microcalcification	n	%	
Yes	8	6.4	
No	117	93.6	
Contour	n	%	
Yes	-	-	
No	125	100	
Increased anteroposterior diameter	n	%	
Yes	5	4	
No	120	96	
FNA (n=78)	n	%	
Benign	75	60	
Malign	2	1.6	
AUS	1	0.8	
Histopathology	n	%	
Benign	9	81.8	
Malign	2	18.2	

SD: Standard deviation, AUS: Atypia of uncertain significance, FNA: Fine needle aspiration, US: Ultrasonography

One of the two patients with histopathologically malignant lesion had a nodule with regular contours, hypoechoic and microcalcification in the lower pole of the left thyroid lobe (size 37*49*52 mm), with regular contours, as US finding, and the result of FNA was also found to be malignant. Post-operative malignant lesion was also detected in the left lobe, consistent with US. The second patient had a histopathologically malignant lesion in the right lobe, and a hypoechoic nodule (16*17*20 mm) was observed only in the lower pole of the left lobe as US finding, and FNA was not performed. In the US evaluation of the nodule of a patient with malignant cytology by FNA, it was observed that the nodule was in the middle lobe of the thyroid, with mixed echogenicity, without microcalcification, with regular contours, and no increase in anteroposterior diameter, and the post-operative histopathological result was found to be benign. The US and FNA characteristics of the thyroid nodules of patients who were found to be histopathologically malignant are summarized in Table 2.

Table 2. Characteristics of the thyroid nodules of patients who were found to be histopathologically malignant

	Patient 1	Patient 2
Age	64	63
Gender	Male	Male
US results		
Thyroid site	Left lower pole	Left lower pole
Echogenicity	Hypoechoic	Hypoechoic
Microcalcification	Yes	No
Increased anteroposterior diameter	No	No
Contour irregularity	No	No
FNA result	Malign	None

FNA: Fine needle aspiration, US: Ultrasonography

DISCUSSION

Thyroid cancer is one of the most common endocrine tumors and its incidence is increasing all over the world. Thyroid nodules, which are mostly detected by physical examination or imaging methods, are detected as the first finding of thyroid cancers (2).The incidence of malignancy in patients with TTN has been reported at different rates in studies. Mohammed et al., Smith et al. and Tam et al. reported that thyroid malignancy rate of TTN patients as 21.43%, 18% and 19.2%., respectively (11-13). Choong et al. (14) in total, seven (4.7%) of the 148 patients were found to have thyroid cancer; 1 (3.2%) of the 31 patients from 1990 to 1999, 3 (4.2%) of the 72 patients from 2000 to 2009, and 3 (6.7%) of the 45 patients from 2010 to 2014. Preece et al. (15) reported this rate as 6.4%. In our study, the malignancy rate in TTN patients was found to be 1.6%, and this rate was found to be lower than other studies. It was thought that this difference in studies could be related to patient selection and method differences, geographical and ethnic differences, iodine status of the population in which the study was conducted, the scope of the surgery (total or hemithyroidectomy) or histopathological examination.

It is known that male gender is a risk factor for thyroid cancer (16). Mohamed et al. (11) found the male sex ratio to be 15.58% in TTN patients who were found to be benign, and 38.1% in those with malignant ones. Smith et al. (12) reported

these rates as 11% and 27%, respectively. In our study, it was observed that both patients (100%) who were found to be malignant were male. These results suggested that male gender may also be a risk factor for TTN related thyroid malignancies.

Being under the age of 20 and being old are known risk factors for thyroid cancer (16). However, Preece et al. (15) reported that the mean age of their patients with thyroid nodules was 54 in both malignant and benign patients. Ozdemir et al. (2) found these averages to be 55.5 and 56, respectively, in their study. The mean age of all patients with TTN in our study was 63.55, and the mean age of the two patients who were found to be malignant was 63.5 years. Age wasn't seen a determining factor in the evaluation of nodules as benign or malignant.

Thyroid US is easy, practical, inexpensive and the most sensitive method for imaging the thyroid gland. With thyroid USG, the size of the thyroid gland, the size of the nodule, its structure (cystic, solid or mixed) and echogenicity (hypoechoic or hyperechoic), calcifications, the status of the lymph nodes can be visualized, and biopsy can be performed on the thyroid nodules under US guidance. In addition, since some findings on US may suggest malignancy, they are effective in the decision of biopsy and surgery (14). Contour irregularity, anteroposterior diameter increase, presence of microcalcification are among these US findings. Ozdemir et al. (2) found these findings at a similar rate in benign and malignant nodules in their study. In our study, there was no increased anterior-posterior diameter and contour irregularity in both patients who were found to be malignant, and only one patient had microcalcification. Ozdemir et al. (2) also found a hypoechoic image on US in 15.38% of the nodules they detected as malignant and in 6.20% of the nodules they detected as benign. Önver et al. (17) reported the presence of hypoechoic nodules on US in 21 (84%) of 25 patients with thyroid nodules that they found to be malignant, and in 22 (40%) of 56 patients they found benign. In addition, the second patient did not have a suspicious appearance, except that he had a hypoechoic nodule. This showed that nodule echogenicity is important in the suspicion of malignancy.

It should be kept in mind that thyroid cancer can be encountered in the contralateral lobe in TTN patients. Tam et al. (13) incidence of cancer detection in the contralateral lobe was 10%, Satta et al. (18) reported this rate as 5%. In our study, malignancy was found in two of 125 patients. In one of these patients, the presence of cancer was reported not in the lobe with active nodule detected by US, but in the contralateral lobe without biopsy indication.

The limited number of patients with toxic thyroid nodules is the limitation of the study.

In conclusion, hypoechoic image in US findings and male gender were considered as risk factors for malignancy in TTN patients.

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RESEARCH ARTICLE

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Factors Affecting Mortality and Patient Outcome in Patients with COPD Followed in The Intensive Care Unit

ABSTRACT

Objective: COPD is characterized by exacerbation and may lead to intensive care unit admission in cases such as pneumonia and sepsis. While non-invasive mechanical ventilation is the first treatment option in intensive care units, it reduces mortality and hospitalization. In our study, we aimed to determine the factors affecting mortality in patients with COPD admitted to intensive care unit.

Methods: In our study, the data of patients admitted to the intensive care unit of Bolu Izzet Baysal State Hospital with COPD were evaluated retrospectively. Duration of intensive care unit stay, APACHE II score, comorbidities, need for noninvasive mechanical ventilation, CRP albumin ratio and leukocyte lymphocyte ratio were recorded.

Results: A total of 416 patients, including 177 (42.5%) women, were included in our study. Of the patients, 107 (25.7%) (Group 1) were admitted to ICU for COPD exacerbation, 183 (44%) (Group 2) for pneumonia and 126 (30.3%) (Group 3) for sepsis. Hypertension was the most common comorbidity in 112 patients (26.9%). Mortality was higher in patients with pneumonia and sepsis than in patients with COPD exacerbation. When all patients were compared according to prognosis, age, length of ICU stay, NLR, CAR and APACHE II scores were higher in patients who died. The duration of non-invasive mechanical ventilation was higher in patients with an episode of COPD, while mortality was higher in patients receiving invasive mechanical ventilation support.

Conclusions: While pneumonia and sepsis increase mortality in patients with COPD, NIMV has a favorable prognosis in these patients with encouraging results.

Keywords: Chronic Obstructive Pulmonary Disease Exacerbation, Non Inasive Mechanical Ventilation, Intensive Care Unit, CRP to Albümin Ratio, Neutrophil to Lymphocyte Ratio.

Yoğun Bakım Ünitesinde Takip Edilen KOAH'lı Hastalarda Mortalite Ve Hasta Sonuçlarını Etkileyen Faktörler

ÖZET

Amaç: KOAH alevlenme ile karakterize olup pnömoni ve sepsis gibi durumlarda yoğun bakım ünitesine yatışa neden olabilmektedir. Non-invaziv mekanik ventilasyon yoğun bakım ünitelerinde ilk tedavi seçeneği olmakla birlikte mortaliteyi ve hastanede kalış süresini azaltmaktadır. Çalışmamızda yoğun bakım ünitesine kabul edilen KOAH'lı hastalarda mortaliteyi etkileyen faktörleri belirlemeyi amaçladık.

Gereç ve Yöntem: Çalışmamızda Bolu İzzet Baysal Devlet Hastanesi yoğun bakım ünitesine KOAH tanısı ile yatırılan hastaların verileri retrospektif olarak değerlendirildi. Yoğun bakımda kalış süresi, APACHE II skoru, komorbiditeler, noninvaziv mekanik ventilasyon ihtiyacı, CRP albumin oranı ve lökosit lenfosit oranı kaydedildi.

Bulgular: Çalışmamıza 177'si (%42,5) kadın olmak üzere toplam 416 hasta dahil edilmiştir. Hastaların 107'si (%25,7) (Grup 1) KOAH alevlenmesi, 183'ü (%44) (Grup 2) pnömoni ve 126'sı (%30,3) (Grup 3) sepsis nedeniyle YBÜ'ye kabul edilmiştir. Hipertansiyon 112 hastada (%26,9) en sık görülen komorbidite olmuştur. Mortalite, pnömoni ve sepsis hastalarında KOAH alevlenmesi olan hastalara göre daha yüksekti. Tüm hastalar prognoza göre karşılaştırıldığında, ölen hastalarda yaş, YBÜ'de kalış süresi, NLR, CAR ve APACHE II skorları daha yüksekti. Non-invaziv mekanik ventilasyon süresi KOAH atağı olan hastalarda daha yüksekken, mortalite invaziv mekanik ventilasyon desteği alan hastalarda daha yüksekti.

Sonuç: KOAH'lı hastalarda pnömoni ve sepsis mortaliteyi artırırken, NIMV bu hastalarda olumlu bir prognoza sahiptir ve cesaret verici sonuçlar vermektedir.

Anahtar Kelimeler: Kronik Obstrüktif Akciğer Hastalığı Alevlenmesi, Noninaziv Mekanik Ventilasyon, Yoğun Bakım Ünitesi, CRP Albümin Oranı, Nötrofil Lenfosit Oranı.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive disease caused by inflammation in the airways, with acute deterioration in lung function and respiratory symptoms, often requiring hospitalization. Although COPD is among the leading causes of morbidity in the world, it is the third most common cause of death in terms of the frequency of causes of death (1).

Since COPD frequently progresses with exacerbations, it causes a significant socioeconomic burden on patients and their relatives (2). Although mortality rates associated with COPD exacerbation vary in various studies, rates ranging between 11% and 32% have been reported (3-7). However, the need for mechanical ventilation is increasing in COPD patients with acute exacerbation (4-8).

Community-acquired pneumonia is one of the most common infectious diseases seen worldwide and ranks 8th among the leading causes of death in the world. Age, male gender, smoking and presence of comorbid diseases have been shown to increase mortality in pneumonia patients.

In COPD patients with pneumonia, mortality rates vary from study to study. Some studies have shown that the presence of pneumonia increases morbidity and mortality, while others have not found a statistically significant difference. The use of noninvasive mechanical ventilation (NIMV) significantly reduces the need for invasive mechanical ventilation in patients with acute exacerbation of COPD. However, the accompaniment of conditions such as pneumonia, ARDS, pulmonary embolism, extrapulmonary sepsis in COPD exacerbation increases the need for invasive mechanical ventilation (4,12).

Sepsis is a dysregulated host response to infection and causes life-threatening organ dysfunction. Underlying comorbidities, corticosteroid use, anticholinergic drug use, smoking history and impaired barrier function in the respiratory tract have been shown to be risk factors for sepsis in patients with COPD (12,13).

The aim of our study was to investigate the mortality difference between patients admitted to the intensive care unit (ICU) due to COPD exacerbation and patients with COPD and concomitant pneumonia or patients hospitalized in the ICU due to COPD and concomitant extrapulmonary sepsis and the factors affecting the course of the disease.

MATERIAL AND METHODS

Data of 416 patients with COPD in Adult ICUs of Bolu Izzet Baysal State Hospital between January 2018 and December 2020 were retrospectively analyzed. Age, gender, duration of ICU stay, comorbidities, discharge status, types of respiratory support, neutrophil lymphocyte ratios (NLR), CRP albumin ratios (CAR), APACHE II scores and ICU hospitalization diagnoses were recorded. Patients were divided into 3 groups according to their hospitalization diagnoses: COPD exacerbation patients with respiratory failure and no signs of infection were divided into group l, COPD+pneumonia patients with respiratory failure according to imaging method and infection parameters were divided into group ll, and COPD+sepsis patients according to infection parameters, hemodynamic instability and culture growth were divided into group lll. Patients with missing data, patients under 18 years of age and patients with Covid-19 were excluded from the study. Bolu İzzet Baysal University Clinical Research Ethics Committee approval was obtained for the study (decision no: 2021/282, date: 21,12,2021).

Results were presented as mean ± SD. SPSS 18.0 package program was used to evaluate the data. $P<0.05$ values were considered significant. Pearson Chi-Square and Fisher's Exact test were used for comparison. Mann-Whitney U analysis with Bonferroni correction was performed to find out which groups were responsible for the differences. Kruskal Wallis H analysis was used in groups that did not show normal distribution.

RESULTS

A total of 416 patients, including 177 (42.5%) women, were included in our study. Of the patients, 107 (25.7%) (Group 1) were admitted to ICU for COPDexacerbation, 183 (44%) (Group 2) for pneumonia and 126 (30.3%) (Group 3) for sepsis. The most common comorbidity was hypertension (HT) in 112 patients (26.9%), followed by diabetes mellitus (DM), heart disease (CH) and malignancy. The mortality rate of the patients included in our study was 39.2%. Of the patients admitted to the ICU, 134 (32.2%) were treated with NIMV only, 48 patients were intubated at the time of ICU admission, and 234 patients were treated with IMV because they were treated with NIMV at the time of ICU admission and failed. The mean age of the patients included in the study was 74.73 (±11.11) years and the mean length of ICU stay was 12.52 (±12.94) days. The characteristics of the patients at admission and follow-up are shown in Table 1.

When we compared the patients according to their hospitalization diagnoses, there was no difference in terms of gender in all three groups, while mortality was significantly higher in group 2 and group 3. When we compared comorbidities, we found that patients with DM were significantly more in group 3. While NIMV success was higher in group 1, more IMV support was required in group 2 and group 3. Comparison of all 3 groups in terms of gender, mortality, comorbidity and respiratory support is shown in Table 2.

Table 1. Characteristics of Cases in Intensive Care Admission and Follow-up

		n	%
Tanı	Group 1	107	25.7
	Group 2	183	44.0
	Group 3	126	30.3
Discharge status	Discharged	253	60.8
	Deceased	163	39.2
Gender	Female	177	42.5
	Male	239	57.5
Comorbidities	HT	112	26.9
	DM	86	20.7
	CD	51	12.3
	Malignancy	32	7.7
Only NIMV		134	32.2
Only lMV		48	11.5
NIMV+lMV		234	56.3
		Mean.±SD	(Min.-Max.)
Age		74.73±11.11	(18-100)
Length of Stay		12.52±12.94	(3-88)
NLR		16.82±19.76	(1-330)
CAR		27.06±25.54	(1-155)
APACHE II		21.38±6.6	(6-38)

NLR: Neutrophil to lymphocyte ratio, CAR: CRP to Albumin ratio, HT: Hypertension, DM: Diabetes mellitus, Cardiac disease, NIMV Non inavasive mechanical ventilation, IMV: Invasive mechanical ventilation

Table 2. Distribution of gender, discharge, comorbidity, NIMV and IMV rates according to groups

		Group 1		Group 2		Group 3		p
		n	%	n	%	n	%	
Gender	Male	59	55.1	102	55.7	78	61.9	0.478
	Female	48	44.9	81	44.3	48	38.1	
Discharge status	Deceased	23	21.5	87	47.5	53	42.1	***0.000***
	Discharged	84	78.5	96	52.5	73	57.9	
Comorbidity		35	32.7	54	29.5	59	46.8	***0.006***
HT		25	23.4	45	24.6	42	33.3	0.148
DM		21	19.6	26	14.2	39	31	***0.002***
CD		14	13.1	19	10.4	18	14.3	0.563
Malignancy		5	4.7	15	8.2	12	9.5	0.362
NIMV		51	47.7	43	23.5	40	31.7	***0.000***
IMV		5	4.7	21	11.5	22	17.5	***0.010***

Pearson Chi-Square

When the relationship between the mortality status of the patients in our study and all 3 groups was analyzed, no relationship was found with gender, while the presence of comorbidity was found to significantly affect mortality. When the three groups were analyzed separately, the presence of DM and HT in group 1 and the presence of all comorbidities in group 2 were associated with mortality. In group 3, comorbidities were not associated with mortality. The comorbidity-mortality relationship in all 3 groups is shown in Table 3.

When the characteristics of the patients according to the groups were analyzed, no significant difference was found in terms of age and length of ICU stay. Group 1 had longer NIMV support, which was associated with benefiting from NIMV and being persistent. While NLR was higher in Group 3, CAR was significantly different in all three groups. APACHE II scores were significantly lower in group 1. The relationship between NIMV, NLR, CAR, APACHE II and length of hospitalization according to the groups is shown in Table 4.

Table 3. Distribution of gender, comorbidity, NIMV, and IMV rates according to the discharge status in all cases and groups

		Discharged		Deceased		p
		n	%	n	%	
All cases						
Cinsiyet	Male	154	60.9	85	52.1	0.079
	Female	99	39.1	78	47.9	
Comorbidity		75	29.6	73	44.8	***0.002***
HT		50	19.8	62	38.0	***0.000***
DM		38	15.0	48	29.4	***0.000***
CD		21	8.3	30	18.4	***0.002***
Malignancy		10	4.0	22	13.5	***0.000***
Group 1						
Gender	Male	50	59.5	9	39.1	0.081
	Female	34	40.5	14	60.9	
Comorbidity		22	26.2	13	56.5	***0.006***
HT		16	19.0	9	39.1	***0.044***
DM		10	11.9	11	47.8	***0.000***
CD		8	9.5	6	26.1	0.073
Malignancy		3	3.6	2	8.7	0.292
Group 2						
Gender	Male	55	57.3	47	54.0	0.657
	Female	41	42.7	40	46.0	
Comorbidity		18	18.8	36	41.4	***0.001***
HT		13	13.5	32	36.8	***0.000***
DM		9	9.4	17	19.5	***0.049***
CD		5	5.2	14	16.1	***0.016***
Malignancy		4	4.2	11	12.6	***0.037***
Group 3						
Gender	Male	49	67.1	29	54.7	0.157
	Female	24	32.9	24	45.3	
Comorbidity		35	47.9	24	45.3	0.768
HT		21	28.8	21	39.6	0.202
DM		19	26.0	20	37.7	0.160
CD		8	11.0	10	18.9	0.210
Malignancy		3	4.1	9	17.0	***0.015***

Pearson Chi-Square, Fisher's Exact test

Table 4. Mean distribution of age, hospitalization duration, NIMV days, NLR, CAR, and APACHE II scores according to the groups

	Group 1		Group 2		Group 3		p
	Mean.±SD	Median (Min.-Max.)	Mean.±SD	Median (Min.-Max.)	Mean.±SD	Median (Min.-Max.)	
Age	73.72±10.33	75 (46-92)	76.04±11.42	78 (18-100)	73.67±11.18	75,5 (22-95)	0.060
Length of Stay	11.17±11.69	7 (3-68)	12.84±12.6	8 (3-86)	13.21±14.36	8 (3-88)	0.192
NIMV day	3.68±2.31	3 (0-11)	2.85±2.2	2 (1-12)	3.05±2.13	2 (1-9)	***0.001***
NLR	15.39±31.62	10 (1-330)	15.23±11.28	12 (1-70)	20.36±15.67	17 (3-90)	***<0.001***
CAR	7.26±9.28	4 (1-60)	31±25.37	30 (1-155)	38.15±25.95	35 (2-150)	***<0.001***
APACHE II	19.55±5.84	18 (10-35)	21.92±7.08	22 (6-38)	22.15±6.21	20 (10-37)	***0.002***

Kruskal Wallis H analizi
NLR: Neutrophil to lymphocyte ratio, CAR: CRP to Albumin ratio

When all patients were compared according to discharge status, age, ICU length of stay, NLR, CAR and APACHE II scores were significantly higher in patients who exited. In surviving patients, the duration of NIMV was significantly higher. The relationship between mortality and variables is shown in Table 5.

Table 5. Mean distribution of age, hospitalization duration, NIV days, NLR, CAR, and APACHE II scores according to the discharge status

	Discharge status				p
	Discharged		Deceased		
	Mean.±SD	Median (Min.-Max.)	Mean.±SD	Median (Min.-Max.)	
Age	73.47±11.06	75 (18-96)	76.69±10.93	79 (41-100)	***0.002***
Length of Stay	9.51±9.06	6 (3-55)	17.2±16.27	12 (3-88)	***0.002***
NIMV day	3.38±2.35	2 (1-12)	21.6±11.82	2 (0-11)	***0.000***
NLR	15.64±22.23	11 (1-330)	18.66±15.03	14 (1-90)	***0.010***
CAR	19.97±19.49	11 (1-150)	38.06±29.67	35 (1-155)	***0.000***
APACHE II	18.55±5.23	18 (6-35)	25.79±6.08	27 (7-38)	***0.000***

Mann Whitney U analizi
NLR: Neutrophil to lymphocyte ratio, CAR: CRP to Albumin ratio

DISCUSSION

COPD is a progressive chronic disease that affects the respiratory system, reduces lung function, and frequently requires hospitalization. When the etiology of hospital admission in patients with severe COPD is analyzed, the most common etiology is COPD exacerbation, followed by pneumonia. The etiology of respiratory failure cannot be determined in 21% of patients (13). In COPD patients, pneumonia has been shown to prolong hospital stay, increase the need for mechanical ventilation, and increase mortality and ICU hospitalization rate (14). Sepsis is a state of dysregulated response to infection with poor long-term patient outcomes, high mortality, high frequency of hospital readmission, and impaired quality of life. Bacterial infections are common in COPD patients, either respiratory or non-respiratory. Underlying comorbidities, corticosteroid use, anticholinergic drug use, smoking history, and impaired barrier function in the respiratory tract have been shown as factors (12,13). In our study, 25.7% patients were followed up due to COPD exacerbation, 44% due to COPD and pneumonia, and 30.3% due to COPD and sepsis. While a mortality rate of 21.5% was found in our patients in the COPD exacerbation group, this rate was lower than in other COPD patients hospitalized with pneumonia or sepsis.

When the factors affecting mortality were evaluated, the duration of ICU stay and mean age were similar between the groups. The mortality rate was found to be higher in patients with comorbidities in terms of comorbidities, and the frequency of comorbidities was higher in group 2 and group 3, where mortality was higher in group 2 and group 3 with pneumonia or sepsis. In particular, it was found that the presence of DM significantly increased mortality and APACHE II scores of COPD patients with sepsis and pneumonia were higher.

In a study, ICU mortality rate was 9% and hospital mortality rate was 17% in patients admitted with COPD exacerbation. Another study found that the mortality rate of patients with a diagnosis of pneumonia and COPD who were followed up in the ICU (30.1%) was higher than those hospitalized for COPD alone (21.4%) (15,16).

Survival was found to be significantly correlated with APACHE II score and presence of active malignancy in ICU patients (16). In our study, the presence of malignancy did not have a significant effect on survival among the 3 groups. However, APACHE II value was found to be significantly lower in patients hospitalized with a diagnosis of COPD exacerbation and mortality was also found to be significantly lower in this group. It was observed that dyspnea and tachypnea developed more frequently in patients hospitalized in the ICU for pneumonia in the presence of male gender, advanced age and smoking. In these patients, the duration of ICU stay was found to be longer and the need for NIMV was also higher. In a 2018 study, hospital mortality of patients hospitalized with COPD and concomitant pneumonia was 8.3% and the 60-day mortality rate of the same group was reported as 12.6% (17). In another study, the 30-day mortality rate was found to be 8.4% in patients diagnosed with COPD and pneumonia, but it was also reported that no mortality difference was found between patients diagnosed with pneumonia alone and patients with COPD (16).

In a study by Keenan et al. it was reported that mortality was higher in patients with a diagnosis of COPD and comorbidities, while in another study by Patil et al. mortality was found to be higher in patients with cardiovascular disease (18,19). In our study, the presence of DM was found to be the most important reason increasing mortality.

Gadre et al. found that the mean number of days of hospitalization due to COPD was 20.7 days and the need for ICU developed in 14.3% of patients (15). In our study, the duration of ICU stay due to COPD exacerbation was found to be 11.17 days. However, no significant difference was found between the ICU length of stay in patients with pneumonia or extrapulmonary sepsis.

In the literature, there is no significant consistency between the ICU mortality rates of

COPD patients. However, there is a consensus that the presence of comorbidity, APACHE II elevation, age, and length of ICU stay affect mortality and morbidity. In addition, not only the ICU follow-up of the patients, but also their post-discharge care, treatment status and measures to be taken to prevent the disease have an effect on mortality and morbidity. In addition, other factors affecting mortality and morbidity include nutritional status of the patient, frequency of hospitalization, smoking status, and changes in lung reserve (10-21).

In the treatment of COPD exacerbation, NIMV is one of the proven methods because it reduces hypoventilation and corrects hypoxemia. In addition, it has been shown to reduce respiratory muscle fatigue by decreasing respiratory workload, decrease airway resistance, provide recruitment of collapsed alveoli and decrease dynamic hyperinflation with applied positive pressure (22,23). It has been found that respiratory acidosis regresses with the use of NIMV and the need for invasive mechanical ventilation decreases even in patients with severe acidosis.(10, 24)

Dai et al. reported that the need for NIMV, ICU admission and APACHE II score were higher in COPD patients admitted to ICU due to pneumonia compared to patients who developed only COPD exacerbation. It was reported that NIMV was associated with 60-day mortality and decreased the rate of intubation. In patients who failed NIMV ventilation and were intubated, the mortality rate reached 50% (17,25).

Gadre et al. found that the rate of invasive mechanical ventilation was lower and the duration of mechanical ventilation was shorter in patients admitted to the ICU due to COPD exacerbationcompared to patients hospitalized in the ICU for other reasons. They stated that pneumonia was the most common cause of clinical deterioration in COPD patients requiring IMV. In the same study, mortality rates were found to be 25% in patients requiring invasive mechanical ventilation and this rate was similar to ICU mortality rates. When COPD patients requiring IMV for other reasons were excluded, they stated that the epidemiology and outcomes of COPD patients could not be fully specified. They explained this situation as COPD being a comorbidity in ICU intubated patients and not the main reason for intubation (15).

There is a reluctance to apply invasive mechanical ventilation in clinicians who follow patients admitted to ICU with a diagnosis of COPD exacerbation. This may be due to the fear that if these patients are intubated, they may not be weaned from the mechanical ventilator for a long time or at all. It has been shown in a study that COPD patients who developed respiratory failure due to other causes and who underwent invasive mechanical ventilation were weaned from the mechanical ventilator for up to 3 days with the application of intermittent spontaneous breathing studies and sedation holidays, and that this period was even shorter in patients who were intubated only because of COPD exacerbation (15). In our study, the rate of NIMV application in patients with a diagnosis of COPD exacerbation only was found to be significantly higher than in COPD patient groups with pneumonia or sepsis. Similar to the aforementioned study, the reason for the insistence on NIMV was the clinician's belief that patients could not be weaned from invasive mechanical ventilation. We also think that this is due to the fact that non-COPD patients do not respond well to NIMV and need IMV support quickly.

In our study, 47.7% of our patients hospitalized with a diagnosis of COPD exacerbation received NIMV and only 4.7% needed invasive mechanical ventilation. 78.5% of these patients were discharged. On the other hand, the need for invasive mechanical ventilation was found to be higher in patients with pneumonia and sepsis.

Chronic inflammation and malnutrition are frequently seen in COPD patients. Therefore, it is thought that CAR may be used as a mortality marker in COPD patients admitted to ICU. In a study by Cırık et al. in which 235 COPD patients were evaluated, it was reported that CAR, APACHE II, duration of mechanical ventilation, WBC, CRP values were higher in patients who died compared to survivors. It has been reported that APACHE II, WBC, CRP and CAR can be used effectively in determining 30-day mortality(26). In other studies, it has been reported that CAR can be used as a mortality marker in critically ill patients with sepsis or septic shock who are followed up with parenteral nutrition (28). In our study, age, ICU length of stay, CAR, NLR and APACHE II values were found to be significantly higher in patients with exitus compared to survivors.

There are studies showing that high NLR in COPD patients is associated with exacerbation and is also an independent risk factor in determining mortality (6-8). NLR is thought to be a new inflammatory marker for the evaluation of inflammation in COPD patients because it is cheap, rapid and easily measurable. In our study, NLR value was found to be significantly higher in patients with exitus. We think that NLR can be used effectively in the evaluation of inflammation and mortality in COPD patients.

The limitations of our study include the fact that it was a single-center, retropective study, functional status, nutritional status, frequency of hospitalization, and smoking status of the patients before hospitalization were not known.

CONCLUSION

COPD is a costly disease that does not only progress exacerbation, and the presence of comorbidities and/or infection can worsen the condition, requiring hospitalization and ICU admission. Sometimes, although COPD is not the

reason for hospitalization, its presence as a comorbidity increases mortality or morbidity. We think that it is indisputably important to know that NIMV reduces the duration of hospitalization, duration of mechanical ventilation and mortality in these patients and to plan NIMV in patient management. Detection of pneumonia or sepsis in COPD patients are important factors that increase the need for invasive mechanical ventilation. Comorbidities such as DM and elevated APACHE II were also found to be factors increasing mortality. We think that the use of markers such as NLR and CAR will be useful in the evaluation of inflammation, detection of exacerbation and evaluation of mortality.

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RESEARCH ARTICLE

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Analysis of the Relation Between the Students' Knowledge on Sexual Health, Opinions on Sexual Myths and Level of Health Literacy

ABSTRACT

Objective: From the public health perspective, young people are considered as a priority group in terms of sexually transmitted diseases and sexual habits. Sexual dimension among adolescents and young adults can be influenced by their overall and sexual health due to its impact on intellectual growth and development and their level of knowledge can significantly affect their reproductive health. The study aims to measure university students' health literacy, sexual health knowledge and sexual myths and in this way explore the relationship between these variables and among various demographic variables.

Methods: The sample of the study is comprised of 559 female and 282 male university students. In the first part, demographic information scale, in the second part sexual health knowledge test, in the third part sexual myths scale, in the fourth part health literacy in Turkey scale were implemented.

Results: In the analysis across the sexes, it was revealed that males have more sexual myths than females ($p<0,05$). In the analysis across the faculties, it was unearthed that students in medical and dental faculties obtained similar points from the scales, but medical faculty students received the highest point and social sciences students received the lowest point. Besides, it was observed that health literacy and sexual health knowledge significantly predicted sexual myths ($p<0,005$).

Conclusions: To this end, it is recommended that consulting services be provided for parents, educational programs be planned for all the departments at university, peer education and supporting programs be implemented and more scientific research be conducted.

Keywords: Health Literacy, Sexual Health Knowledge, Sexual Myths, University Student.

Öğrencilerin Cinsel Sağlık Bilgileri, Cinsel Mitler Hakkındaki Görüşleri ve Sağlık Okuryazarlığı Düzeyleri Arasındaki İlişkinin İncelenmesi

ÖZET

Amaç: Halk sağlığı açısından gençler, cinsel yolla bulaşan hastalıklar ve cinsel alışkanlıklar açısından öncelikli bir grup olarak kabul edilmektedir. Ergenler ve genç yetişkinler arasındaki cinsel boyut, entelektüel büyüme ve gelişme üzerindeki etkisi nedeniyle genel ve cinsel sağlıklarından etkilenebilir ve bilgi düzeyleri üreme sağlıklarını önemli ölçüde etkileyebilir. Çalışma, üniversite öğrencilerinin sağlık okuryazarlığı, cinsel sağlık bilgisi ve cinsel mitlerini ölçmeyi ve bu şekilde bu değişkenler ile çeşitli demografik değişkenler arasındaki ilişkiyi keşfetmeyi amaçlamaktadır.

Gereç ve Yöntem: Araştırmanın örneklemini üniversite öğrencilerinden 559 kadın ve 282 erkek oluşturmaktadır. Birinci bölümde demografik bilgi ölçeği, ikinci bölümde cinsel sağlık bilgisi testi, üçüncü bölümde cinsel mitler ölçeği, dördüncü bölümde Türkiye'de sağlık okuryazarlığı ölçeği uygulanmıştır.

Bulgular: Cinsiyetler arası analizde erkeklerin kadınlara göre daha fazla cinsel mite sahip olduğu ortaya çıktı. Fakülteler genelinde yapılan analizlerde tıp ve diş fakültesi öğrencilerinin ölçeklerden benzer puanlar aldıkları ancak en yüksek puanı tıp fakültesi öğrencilerinin, en düşük puanı ise sosyal bilimler öğrencilerinin aldığı ortaya çıktı. Ayrıca sağlık okuryazarlığı ve cinsel sağlık bilgisinin cinsel mitleri anlamlı düzeyde yordadığı görülmüştür.

Sonuç: Bu amaçla velilere yönelik danışmanlık hizmetlerinin verilmesi, üniversitedeki tüm bölümlere yönelik eğitim programlarının planlanması, akran eğitimi ve destekleyici programların uygulanması ve daha fazla bilimsel araştırma yapılması önerilmektedir.

Anahtar Kelimeler: Sağlık Okuryazarlığı, Cinsel Sağlık Bilgisi, Cinsel Mitler, Üniversite Öğrencisi.

INTRODUCTION

From the public health perspective, young people are considered as a priority group in terms of sexually transmitted diseases and sexual habits. Sexual dimension among adolescents and young adults can be influenced by their overall and sexual health due to its impact on intellectual growth and development and their level of knowledge can significantly affect their reproductive health (1). However, it is stated in the literature that health literacy among university students is poor, sexual myths are quite common and they have very limited and inaccurate sexual knowledge (2). Besides, it is recorded in some studies that sociodemographic factors like being religious, the sexual habits existing in the school, family members and peers shape sexual health knowledge, attitude and habits (3).

Sexual health and reproductivity health encompasses the subjects of being informed about and having access to the services of contraception and treatment methods, methods of contraception that individual use, sexually transmitted diseases, pregnancy, abortion and postpartum services (4). 500 million new cases of sexually transmitted diseases are detected every year. Besides, unplanned and unwanted pregnancies, which account for 60% of the total number of pregnancies, is one of the common health issues observed frequently (5). The young people whose level of knowledge on sexuality is poor are at a higher risk regarding this issue (6). Risky sexual acts or behaviour are frequently observed among university students both in developing and developed countries. The reasons underlying this phenomenon have multiple factors. Studies showed that individuals in this age group do not have sufficient knowledge on reproductivity health, symptoms and implications and probably have false beliefs which can influence their risk-taking behaviour (7–9). In addition, socio-economic change, along with the marrying-late trend, has led to an increase in sexual activity and number of partners before marriage, particularly in developed countries (10).

Sexual myths emerge along with the social values resulting from various factors such as not talking about or discussing the subjects related to sexuality in an explicit manner and inadequate amount of scientific research on this issue (11). Myths negatively influence the individuals' expectations about sexuality, their sexual activities and sexual identity growth. Sexual dysfunctions and psychological problems that emerge along with them develop due to the sexual myths. Sexual myths among young people are closely associated with their level of knowledge on sexual health and the reliability of their sources of information. Although parents and schools are crucial sources of information on sexuality, they both play quite a passive role in Turkey (12). It has been uncovered in several studies that because parents in Turkey are paternal and conservative in nature and the education given in the schools on this subject is not systematic and sufficient, young people in Turkey receive information about sexuality from their peers. The emergence of sexual myths in the case of parents' not having sufficient knowledge on sexuality has brought the significance of educating peers under the spotlight (13-18).

In summary, the data regarding the knowledge level that young people possess on sexual health and reproductive health is of vital importance to establish a healthy society with a higher awareness and to plan effective programs in the universities. The purpose of this study is to (1) identify and evaluate the sexual literacy of university students; (2) identify the experiences and knowledge of university students on sexual health and reproductive health and (3) explore the predictive effect of sexual myths on the university students' health literacy and their knowledge on sexual health.

MATERIAL AND METHODS

Ethics: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Ankara Medipol University (Date 15.08.2022 /No 153).

Research Design: Qualitative research-Correlational research method. The research was conducted in line with a "correlational scan model" as a general scan model.

Population-Sample: The study was carried out in the fall semester of 2022-2023 academic year including the students studying in minimum 4-year faculties in Ankara Medipol University.

The sample of our study constitutes the whole population in our study:

- Small number of students in our university
- The use of hybrid instructional model due to the pandemic
- Aiming to generalize the findings of our study

Data Collection: Face-to-face questionnaire method has been used for the present study to collect data. All the students were informed in detail prior to the study, and they signed the consent form. It was also stated that all the data was unique to the current study. The research is comprised of 4 parts. In the first part, demographic information scale, in the second part sexual health knowledge test, in the third part sexual myths scale, in the fourth part health literacy in Turkey scale were implemented.

Sexual Health Knowledge Test (SHKT): The test was developed by Evcili and Gölbaşı (2017). It involves 40 questions including 12 subdimensions. These dimensions include universal values about sexuality (items 1 and 2), sexual identity development (items 3, 4, 5 and 10), sexual tendencies (items 6, 7 and 14), gender-social gender

(items 8, 9 and 11), anatomy of reproductive system (items 12, 13 and 20), sexual intercourse/sexual satisfaction (items 15, 16, 17 and 21), physiology of reproduction (items 18, 19 and 22), contraception (items 23, 24, 25, 26, 27 and 28), sexually transmitted infections (29, 30, 31, 32, 33, 34 and 35), sexual violence (items 36, 37 and 38) and safe sexual behavior (items 39 and 40). The items that the participants answered correctly are coded as "1". The items that the participants answered incorrectly, and the missing responses are coded as "0". The lowers score possible in SHKT is 0 and the highest point is 40 points. It is accepted that the higher the score is, the more knowledge an individual has about sexual health. Cronbach alpha reliability coefficient was calculated as 0.88. It was shared that the test has high internal reliability. In our study, the Cronbach alpha coefficient of the test was calculated as 0.884.

Sexual Myths Scale (SMS): It was developed by Gölbaşı et al. (2016) and it involves 28 likert scale items. The scale includes 8 sub-dimensions which aresexual tendency (item 15), social gender (items 6-11), age and sexuality (items 12-15), sexual behaviour (items 16-18), masturbation (items 19-20), sexual violence (items 21-24), sexual intercourse (items 25-26) and sexual satisfaction (items 27-28). Sexual myths scale involves the options of "Completely disagree (1), Disagree (2), Undecided (3), Agree (4), Completely agree (5). Cronbach alpha coefficient of the scale is 0.91 (18). In our study, Cronbach alpha coefficient is reported as 0.874.

Turkey Health Literacy Scale-32 (THLS-32): The adaptation of the Eropean Health Literacy Scale, developed using the integrated health literacy model by Ölçek Sorensen, into Turkish and its reliability and validity study was conducted by Pınar Okyay and Filiz Abacıgil. The reliability of the scale in Turkish was calculated as 0.927 (9). It has two dimensions of protection from illnesses and health improvement, three dimensions of having access to health-related information, understanding, evaluating and implemention and a matrix structure of 2x4. Index point calculation method was used to obtain a staard point. Index point refers to an individual's health literacy and its average is calculated based on the points an individual obtained from the items answered. In conclusion, every participant receives a point ranging from 0 and 50. For our study, Cronbach alpha coefficient of the scale was calculated as 0.914.

RESULTS

66.5% of the students included in the study are female and 33.5% of them are male. On a different note, 35.8% of the participants study in the Faculty of Medicine; 24.5% of them in the Faculty of Dentistry, 16.3% of them in the Faculty of Health sciences and 23.8% of them in the Faculty of Social sciences (Law+Faculty of Humanities). 34.4% of the students expressed that they had gained information about sexuality firstly from their friends and 51.4% of them stated that they did not find the information they had about sexuality sufficient (Table 1).

It was observed that the students participating in the study had insufficient health literacy in general and, in particular, they did not have adequate knowledge about health processes, treatments, services and protection (Fig. 1).

Table 1. Descriptive information about the participants

		n	%
Gender	Female	559	66.5
	Male	282	33.5
Faculty	Medicine	301	35.8
	Dentistry	203	24.1
	Social (Law+FOH)	200	23.8
	Faculty of health sciences	137	16.3
How did you learn about sexuality first?	Mother	116	13.8
	Father	20	2.4
	Sibling	47	5.6
	Friend	289	34.4
	TV	8	1.0
	Internet	224	26.6
	School	98	11.7
	Health personnel	5	.6
	Other	34	4.0
Do you find your knowledge about sexuality sufficient?	Yes	432	51.4
	No	407	48.4
Do you talk about sexual health and reproductive health with your family?	No	317	37.7
	Only with my father	294	35.0
	Only with my mother	35	4.2
	With my mother and father	92	10.9
	With my elder sister and brother	103	12.2

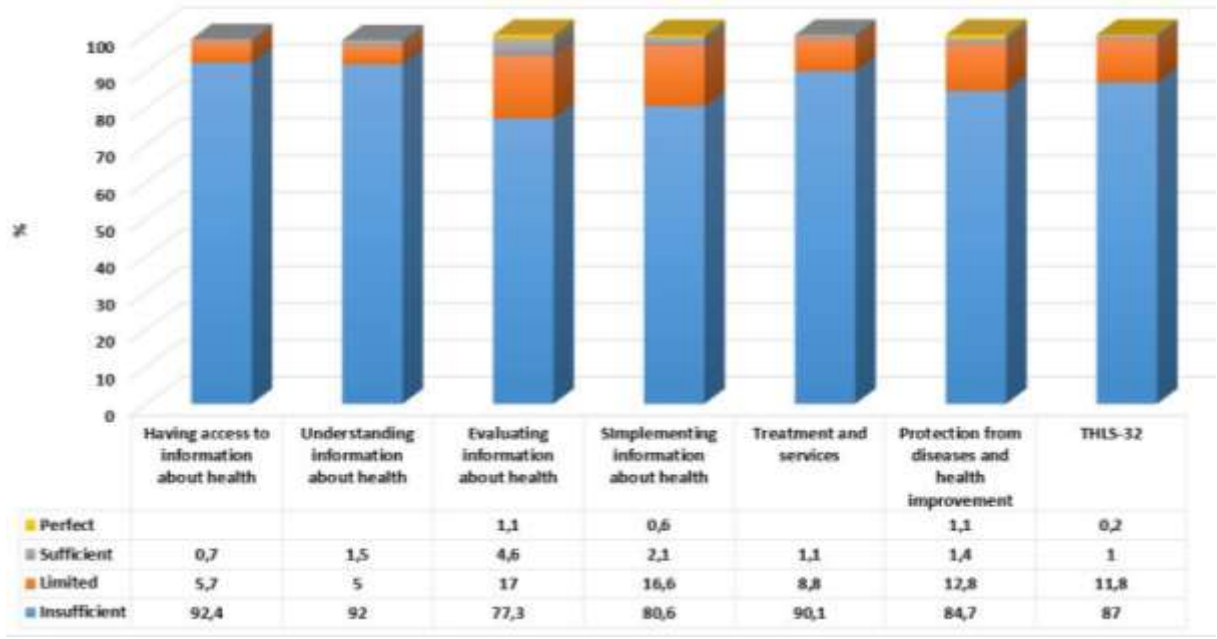

Figure 1. Health literacy levels of participants according to the processes and sub-dimensions in THLS-32 scale.

Table 2 displays the relationship between gender and scales. According to the table, males are more knowledgeable about the processes of THLS 32, treatment and services. Besides, as for the SHK dimensions, the total score of males on sexual identity development, social gender, reproductive system anatomy and physiology is relatively higher than females and there is a statistically significant difference.

Table 2. The compare between gender and scales

		MEAN±SS	FEMALE	MALE	T	P
THLS-32 PROCESSES	Having access to health-related information	14.45±6.30	14.26±8.23	14.83±8.03	-.95	.34
	Understanding health-related information	14.56±5.29	14.31±8.12	15.07±8.59	1.25	.20
	Evaluating health-related information	19.85±4.51	19.84±9.90	19.88±8.70	-.06	.94
	Implementing health-related information	18.52±6.79	18.47±8.91	18.63±7.56	-.25	.79
THLS-32 DIMENSIONS	Treatment and Service	16.15±7.77	15.73±7.83	16.99±5.55	-2.21	**.02***
	Protection from illnesses and health improvement	17.76±5.21	17.68±7.04	17.91±6.53	-.06	.74
THLS-32 TOTAL		16.81±7.86	16.62±7.56	17.19±7.72	-.23	.79
SHK DIMENSIONS	Universal values related to sexuality	1.77±.48	1.76±.49	1.77±.34	-.10	.91
	Sexual identity development	2.16±.82	2.20±.65	2.06±.79	2.40	**.01***
	Sexual tendencies	2.23±.72	2.24±.70	2.22±.77	.34	.73
	Gender-social gender	2.39±.75	2.43±.74	2.30±.76	2.39	**.01***
	Anatomy of reproductive system	2.22±.68	2.26±.70	2.15±.64	2.10	**.03**
	Sexual intercourse/sexual satisfaction	3.34±.91	3.36±.92	3.24±.89	1.08	.29
	Reproductive physiology	2.58±.64	2.65±.60	2.45±.70	4.29	**.00***
	Contraception	4.50±1.38	4.52±1.32	3.34±1.01	.46	.64
	Sexually transmitted infections	4.32±1.07	4.32±1.42	4.33±1.09	-.15	.87
	Sexual violence	2.64±.69	2.66±.76	2.59±.75	1.43	.15
	Safe sexual behavior	1.41±.44	1.41±.64	1.42±.65	-.23	.82
SHK TOTAL		29.36±5.54	29.66±5.49	28.75±5.62	2.25	**.02***
SMS DIMENSIONS	Sexual tendency	10.92±3.86	10.33±4.47	12.09±5.43	-4.99	**.00***
	Social gender	9.27±3.26	8.38±3.44	11.04±5.90	-8.24	**.00***
	Age and sexuality	7.64±3.37	7.08±2.93	8.74±3.86	-6.90	**.00***
	Sexual behavior	4.63±2.55	4.23±2.17	5.41±3.02	-.65	**.00***
	Masturbation	5.80±2.96	4.37±2.20	4.71±2.38	-2.09	**.04***
	Sexual violence	5.80±2.96	5.47±2.55	6.47±3.55	-4.56	**.00***
	Sexual intercourse	4.26±1.99	4.11±1.93	4.54±2.07	-2.91	**.00***
	Sexual satisfaction	4.00±1.80	3.84±1.80	4.31±1.93	-3.45	**.00***
SMS TOTAL		50.60±18.21	47.35±10.09	57.04±12.78	-7.52	**.00***

Test: Independent t test. $p<0.05$

Considering the relationship between the scales and the faculties that participants study, it was observed that the students studying the faculties of Medicine and Dentistry have similar levels of knowledge. Howbeit, the students in the Faculty of Medicine receive relatively higher points in the scales and the students in the faculty of social sciences have the lowest points (p<0,05) (Table 3).

Table 3. The relationship between scales and faculties

		MEDICINE (I)	DENTISTRY (II)	HEALTH SCIENCES	SOCIAL (LAW+FOH)	F	P
THLS-32 PROCESSES	Having access to health-related information	14.94±8.58	15.25±8.20	13.98±7.67	13.32±7.70	2.30	.07
	Understanding health-related information	14.78±8.34	15.45±8.38	14.32±8.33	13.51±8.01	1.94	.12
	Evaluating health-related information	20.29±9.61	20.78±9.31	19.26±9.68	18.67±9.36	2.07	.10
	Implementing health-related information	19.50±8.94	19.92±9.11	17.18±7.94	16.56±8.36	**7.94**	**.00 (I-III. IV; II-**
THLS-32 DIMENSIONS	Treatment and Service	16.95±7.89	16.83±8.14	15.13±7.26	15.02±7.25	**3.69**	**.01 (I-III. IV; II-III.IV)**
	Protection from illnesses and health improvement	18.04±9.25	18.89±9.68	17.20±8.71	16.56±8.72	2.43	.06
THLS-32 TOTAL		18.32±6.21	17.42±8.04	16.15±7.23	15.23±7.58	**5.01**	**.00 (I-III. IV. II-IV)**
SHK DIMENSIONS	Universal values related to sexuality	1.77±.49	1.81±.48	1.82±.41	1.68±.40	**3.44**	**.01 (I-IV. II-IV. III-IV)**
	Sexual identity development	2.22±.82	2.21±.79	2.34±.81	1.88±.82	**10.82**	**.00 (I-IV. II-IV. III-IV)**
	Sexual tendencies	2.35±.69	2.29±.70	2.16±.74	2.02±.76	**7.66**	**.00 (I-IV. II-IV)**
	Gender-social gender	2.41±.72	2.40±.72	2.40±.77	2.32±.81	.70	.54
	Anatomy of reproductive system	2.26±.66	2.24±.66	2.13±.70	2.21±.70	1.05	.35
	Sexual intercourse/sexual	3.42±.87	3.38±.89	3.29±.90	3.21±.58	2.31	.07
	Reproductive physiology	2.66±.58	2.65±.68	2.51±.65	2.41±.73	**6.15**	**.00 (I-III.IV; II-IV)**
	Contraception	4.63±1.41	4.64±1.21	4.37±1.43	4.26±1.21	3.92	**.00 (I-IV. II-IV)**
	Sexually transmitted infections	4.49±1.38	4.58±1.38	4.07±1.56	3.93±1.51	8.97	**.00 (I-III.IV; II-III.IV)**
	Sexual violence	2.68±.67	2.68±.64	2.53±.77	2.60±.72	1.93	.12
	Safe sexual behavior	1.39±.65	1.43±.64	1.42±.62	1.43±.54	.21	.88
SHK TOTAL		30.33±4.87	30.33±4.51	28.89±5.21	27.33±5.65	**15.42**	**.00 (I-IV. II-IV)**
SMS DIMENSIONS	Sexual tendency	9.25±3.63	11.49±5.20	11.03±5.21	12.27±4.63	**12.77**	**.00 (I-III. IV; II-IV)**
	Social gender	8.34±3.10	9.07±2.79	9.69±5.12	9.70±5.29	**4.30**	**.00 (I-IV. II-IV)**
	Age and sexuality	7.01±2.83	7.53±2.99	7.77±3.49	7.97±2.72	**2.93**	**.00 I-IV. II-IV)**
	Sexual behavior	4.32±1.99	4.83±2.82	4.72±2.79	4.57±2.27	1.52	.20
	Masturbation	4.31±2.26	4.40±2.32	4.00±2.19	4.99±2.14	.78	.50
	Sexual violence	5.77±3.25	5.58±3.25	6.10±2.56	5.61±2.31	.46	.70
	Sexual intercourse	4.21±2.03	4.20±2.01	4.28±1.21	4.26±1.92	.89	.65
	Sexual satisfaction	3.91±1.87	3.89±1.87	4.07±1.12	4.24±1.12	1.28	.25
SMS TOTAL		46.05±14.12	48.76±19.54	51.66±20.16	53.12±12.34	**5.82**	**.00 I-IV. II-IV**

Test: One-way Anova. Bonferroni p<0.05

There is a very weak positive correlation between SHKT total score and THLS-32 but a weak positive correlation between SMS total score and THLS-32 and a moderate negative correlation between SHKT and SMS total scores (p<0,05). In the model developed based on Sexual Health

Knowledge scores, it was identified that they significantly predict sexual myths (F (1,106)= 94,709, p<.05). In this model, Sexual Myths scores account for the 10% of the variance (R2adj=.100). Considering the regression coefficients, Sexual Health Knowledge scores (β= -1.04, p< .05) negatively predict Sexual Myths scores (Table 4).

In the model developed based on health literacy scores, it was witnessed that these scores significantly predict Sexual Myths scores (F (1,113)= 24,345, p<.05). In this model, Sexual Myths account for the 5% of the variance in the scores (R2adj=.057). Considering the regression coefficients, it was observed that health literacy knowledge (β= -,389, p< .05) positively predict Sexual Myths (Table 4).

Table 4. Predictive Level of Sexual Health Knowledge and value of health literacy scale for Sexual Myths

Dependent variable	Predictive variable	B	SE	*β*	T	P
Sexual myths	Fixed	81.262	3.202	-.318	25.364	.000
	SHK	-1.040	.101		-9.237	.000
R==.318; R^2=.101; Adj R^2=.100. p<0.05						
Sexual myths	Fixed	44.071	1.462	.168	30.140	.000
	THLS-32	.389	.079		4.934	.000

R==.128; R^2=.058; Adj R^2=.057. p<0.05

DISCUSSION

This study was designated so as to be able to measure university students' health literacy, sexual health knowledge and sexual myths and explore the relationship between these and other demographic variables.

The findings of the present study are in line with the prior studies in terms of sociodemographic factors (14–16). It was found out that university students, influenced by various sociodemographic factors, gain health and sexual knowledge primarily from their friends at school and the internet. These students obtained their knowledge mainly from their peers or mass communication tools rather than their teachers and parents. A great deal of research in the literature casted light on that especially young people studying at university prefer to learn about health and sexuality from their friends and social media, not from their teachers and family (15,17). Having similar findings, the present study showed that young people do not often prefer parents as parties to communicate with since they can interact with others more easily and comfortably without being judged, feeling embarrassed or any kind of prejudice.

A study conducted on health literacy among adults unveiled perfect scores of 19.9% for treatment and service subdimension, perfect scores of 15.6% on health improvement subdimension and poor scores of 19.1% on THLS-32 (18). Our study revealed that the rate of students having perfect literacy on both subdimensions is quite low. 80-90% of them are 'incompetent' on both of the subdimensions. In the Turkey health literacy study, it was declared that 27.1% of the individuals are not competent in treatment and service subdimension, and 37.4% of them are not competent in the subdimension of protection from illnesses and health improvement (19). In many studies done in foreign countries, it was reported that young people have a lot of gaps in their health literacy and sexuality knowledge compared to adults and they have quite false beliefs and attitudes (3,20). In a cross-sectional study done in Pekin, it was revealed that the university students having high-risk sexual behavior and attitude tend to have limited knowledge and methods (21,22). It has been announced that in most of the developing countries, people have limited knowledge on sexual health and reproductive health (23,24). Insufficient knowledge among young people on sexual health may lead to risky behavior, unsafe sexual practices, sexually transmitted diseases, and unwanted pregnancies. In summary, the study revealed that undergraduate students have poor knowledge level of sexual health and reproductive health, and their health literacy knowledge level is incomplete and not adequate.

Considering health literacy processes, it was observed that the most incompetent process is 'having access to health-related information' and the most competent process, compared to the others, is 'evaluating the health-related information'. In the studies conducted by (18,25–27) it was stated that the most incompetent process is 'evaluating health-related information'. A limitation that draws attention is that the studies conducted on the health literacy based on processes were generally university theses and this topic has not been investigated in other studies. The process of evaluating health-related information requires reasoning ability and comes after having access to health-related information and understanding it. For an individual to do evaluation, he first needs to have comprehensive knowledge on a certain subject and then the ability to make a decision suitable for himself. Higher incompetence in evaluation process may be accounted for its being relatively difficult compared to the other processes. In our view, the most important reason why we obtained different results in our study is that our sample is mainly comprised of Medical and Dental students. Although the students are freshmen and sophomores, they may have more competence in

evaluating health-related information as they gained a certain level of knowledge, and we think this may have affected the mean.

Among the processes in THLS-32, it was observed that men are more knowledgeable than women about treatment and service. Similarly, it was revealed that men's total scores and their scores on sexual identity development, social gender, the anatomy, and physiology of reproductive system, as the SHK processes, are higher than women and show a statistically significant difference. Besides, it was also observed that men have more sexual myths than women in all the subdimensions. While there are studies in the literature underpinning that there is no difference across genders in terms of health literacy, sexual knowledge and sexual myths (28), there also studies reporting that women have greater and more accurate knowledge health knowledge and sexual knowledge, but men have more sexual myth beliefs (29,30). Therefore, these differences in health and sexuality may vary depending on the population.

One of the most valuable aspects of this study is that it aims to explore health literacy, sexual health knowledge and perspectives on sexual myths with reference to the faculty that participants study. The reason behind this is that, as a common belief, the health knowledge of the students studying in Medicine and other branches of health is expected to be significantly different from other students. That being said, the findings of the studies revealed that the knowledge of medical/dental students differ from social and health sciences only in certain areas. The difference can be observed in various subdimensions including implementing health-related information, treatment and service, universal values related to sexuality, sexual identity, social gender, sexual satisfaction, physiology of reproduction, infectious diseases, and sexual myths. Medical and dental students received relatively higher scores on these subdimensions compared to the students studying in the fields of health and social sciences and they have a smaller number of sexual myths. The results showed that students in Medicine and Dentistry do have similar knowledge; medical students received high score in the scales and students in the faculties of social sciences received the lowest grades. Soleymani et al. (31) and Regmi et al. (23) emphasized that the students studying in the health-related faculties possess greater knowledge on health literacy and sexual health compared to the students studying in other faculties, but their knowledge level is still not at the desired level. Apparently, university students do not have sufficient knowledge on sexual health and sexual myths. Besides, it is thought that there are other factors like religious values and cultural sensitivities which may affect sexual knowledge level. Topics related to sexuality are still considered as a taboo in the society and students have a great deal of false and incomplete knowledge about these topics as they are not exposed to them in a healthy way.

In our study, it was identified that sexual health knowledge accounts for 10% of sexual myths and health literacy accounts for 5% of sexual myth variance. It was also seen that although sexual health knowledge level and health literacy knowledge level do not have a strong predictive power on sexual myths and beliefs, they do influence these myths to a certain extent. The reason behind this is that knowledge and attitude are two parameters that are closely linked to each other. The more an individual becomes knowledgeable on a certain topic, the less prejudices, false information, and myths he will have. Our study showed a positive correlation between health literacy and sexual health knowledge but a negative correlation between sexual health knowledge and sexual myths. In other words, the higher sexual health knowledge one has, the less sexual myths and myth beliefs on sexual tendencies he will have. Related to this, Evcili and Gölbaşı (13) and Kocagöz (32) pinpointed in their study that there is a positive correlation between health literacy and sexual health knowledge and a negative correlation between sexual health knowledge level and sexual myths

Limitations

The limited sample size of the study group is the biggest limitation of the study. In addition, the study can be repeated with different samples.

CONCLUSION

In conclusion, it was observed that health literacy among university students, sexual health knowledge and sexual myths are closely linked to each other. On a different note, the predictive effects of health literacy and sexual health knowledge on sexual myths was confirmed in the present study. In the case of a strong connection between sexual knowledge level and sexual myths, providing sexual health knowledge for the young people has an influential role in reducing sexual myths. Therefore, ultimate attention should be paid to exploring the factors which cause the prejudgments resulting from sexual myths in the society and limitations of the healthcare system.

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RESEARCH ARTICLE

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Emergency Department Neurosurgical Consultations in a Tertiary Care Hospital

ABSTRACT

Objective: To reveal the characteristics of patients in need of neurosurgery by examining neurosurgery consultations within the emergency department (ED) admissions of a tertiary academic hospital.

Methods: This is a retrospective, single-centre observational study. Patients admitted to the ED between 01.01.2022 - 31.12.2022 and consulted to the neurosurgery department were identified through the hospital computer system and included in the study. The demographic information of the patients, mode of admission to the ED, the reasons for admission, the time of admission, the number of brain computed tomography (CT) scans, whether they underwent surgery or not, and the mortality results were recorded.

Results: A total of 441 neurosurgery consultations were examined. Fall 35.6% (n=157) and traffic accident 16.6% (n=73) were the most common reasons for consultation. It was observed that 92.5% (n=408) of the patients had a brain CT scan, and 19.5% (n=86) had two or more brain CTs. It was determined that 12.7% (n=56) of the patients consulted to neurosurgery were operated on, and 4.1% (n=18) of the patients' hospital admissions resulted in death. Only 53.7% (n=237) of the patients who underwent neurosurgery consultation were discharged from the ED. It was determined that significantly more Neurosurgery consultations were requested during working hours (p = 0.013).

Conclusions: Most consultation calls from the ED to neurosurgery are for trauma patients. Brain CT examination is frequently used in neurosurgical patient evaluation. As a result of the consultations, almost half of the patients are hospitalized. Emergency physicians can select patients who need neurosurgery well.

Keywords: Emergency Department, Neurosurgery, Consultation.

Üçüncü Basamak Bir Hastanede Acil Servis Nöroşirurji Konsültasyonları

ÖZET

Amaç: Üçüncü basamak akademik bir hastanenin acil servis başvuruları içerisindeki nöroşirürji konsultasyonlarının incelenerek nöroşirürji ihtiyacı olan hastaların özelliklerinin ortaya konulması amaçlandı.

Gereç ve Yöntem: Bu retrospektif, tek merkezli gözlemsel bir çalışmadır. 01.01.2022 – 31.12.2022 tarihleri arasında acil servise başvuran ve acil servisten beyin cerrahi bölümüne konsulte edilen hastalar hastane bilgi işlem sistemi üzerinden tespit edilip çalışmaya dahil edildi. Hastaların demografik bilgileri, hastaneye başvuru şekilleri, başvuru nedenleri, başvuru saatleri, çekilen beyin bilgisayarlı tomografi (BT) sayıları, ameliyat olup olmadıkları ve mortalite sonuçları kaydedildi.

Bulgular: Acil servisten bir senede toplamda 441 nöroşirürji konsültasyonu yapıldı. Düşme %35,6 (n=157) ve trafik kazası %16,6 (n=73) en sık konsültasyon sebepleriydi. Hastaların %92,5 (n=408) ‘ine beyin BT çekildiği, %19,5 (n=86) hastaya ise 2 ya da daha çok beyin BT tetkiki yapıldığı görüldü. Nöroşirürjiye konsulte edilen hastaların %12,7 (n=56) ‘sının ameliyat edildiği, %4,1 (n=18) ‘inin hastane başvurusunun eksitus ile sonuçlandığı saptandı. Nöroşirürji konsültasyonu yapılan hastaların sadece %53,7 (n=237) ’si acil servisten taburcu oldu. Mesai saatleri içerisinde anlamlı olarak daha fazla Nöroşirürji konsültasyonu yapıldığı tespit edildi (p=0.013).

Sonuç: Acil servisten nöroşirürjiye yapılan konsültasyon çağrılarının büyük çoğunluğu travma hastaları içindir. Nöroşirürjik hasta değerlendirmesinde sıklıkla beyin BT tetkikinden yararlanılmaktadır. Yapılan konsültasyonlar sonucunda hastaların neredeyse yarısı hastaneye yatırılmaktadır. Acil servis hekimleri nöroşirürji ihtiyacı olan hastaları iyi seçebilmektedir.

Anahtar Kelimeler: Acil Servis, Nöroşirürji, Konsültasyon.

INTRODUCTION

Emergency department (ED) constitute the most accessible step in the health systems all over the world due to their ease of access, their ability to be applied without an appointment and their 24-hour service. This accessibility is life-saving in medical situations requiring rapid intervention. Failure of other steps of the health system to provide adequate service makes EDs the safety valve of the health system. ED crowding reduces speed and accessibility, which are life-saving features of the ED. ED crowding is a public health problem worldwide (1).

Millions of ED visits are made in Türkiye every year (2). The majority of these admissions are green triage coded patients. It is possible to complete the examination and treatment of many patients in the ED and discharge them, but some patients need to be consulted with other departments in terms of both treatment recommendation and hospitalisation planning. In a study, it was shown that urgent consultation was required in the management of 10-40% of patients evaluated in the ED (3-5). Studies have shown that the time elapsed during the request for consultation, arrival of the consultant physician in the ED, evaluation of the patient by the consultant physician and making recommendations by the consultant physician is 33-54% of the total length of stay (LOS) in the ED (6). It is essential to consult the appropriate patient with the appropriate department by providing the necessary information completely. Unnecessary consultations will increase LOS and cause ED crowding (7). Precautions such as shortening the response time of the consultant and the time to reach the ED, identifying patients who will need consultation earlier and requesting consultations without wasting time can also be applied to decrease LOS (4).

Neurosurgery department (NSD) is one of the most consulted departments from ED. It is one of the departments with the highest number of emergencies with traumatic and non-traumatic emergency cases. However, even in developed countries, there is 1 neurosurgeon per 80.000 people. This rate drops to 1 neurosurgeon per 1 million people in African countries (8). Correct determination of the indications for consultation, performing the necessary examinations before consultation and presenting the patients to the consultant physician appropriately will reduce the loss of time and effort (3).

This study aimed to reveal the characteristics and clinical outcomes of patients who presented to the emergency department of a tertiary academic hospital and underwent neurosurgery consultation. The data to be obtained as a result of the study are expected to contribute to the establishment of a more efficient consultation system. It aims to analyze the data of the consulted patients in terms of both ED and NSD and to shed light on planning interventions that will increase the quality of service.

MATERIAL AND METHODS

Study Setting and Design: This is a retrospective, single-centre observational study. It was conducted in ED of a tertiary university hospital in Türkiye, with approximately 90,000 admissions per year. After obtaining local ethics committee approval (2023/110, 10.07.2023), patients admitted to the emergency department between 01.01.2022 - 31.12.2022 and consulted to the NSD from the ED were identified through the hospital computer system and included in the study.

Multiple NSD consultations in the same admission were considered as a single consultation. Demographic information of the patients, method of admission, reasons for admission, time of admission, number of brain computed tomography (CT) scans, data of whether they underwent surgery or not, and mortality results were obtained from the hospital computer system and archive records and recorded in the study form.

Selection of Participants and Study Protocol: Patients who presented to the ED and were consulted to NSD for any reason within a one-year period were included in the study. Three patients were excluded from the study because they left the hospital voluntarily before the consultation was completed and four patients were excluded because they refused hospitalisation although they were offered hospitalisation.

The patients were divided into three groups according to the time of admission: patients who admitted between 24:00 - 08:00 were grouped as shift 1, patients who admitted between 08:00 - 16:00 were grouped as shift 2, and patients who admitted between 16:00 - 24:00 were grouped as shift 3. It was analysed whether there was any difference between the groups in terms of gender, complaint, hospitalisation status and mortality.

Data Analysis: Statistical software SPSS version 23 (SPSS Inc., Armonk, NY) was used for these analyses. Countable data were summarised as median (25th and 75th percentile), and categorical data as frequency and percentage. Countable data were compared between the two groups by Mann-Whitney U test. The relationship between two categorical variables was analysed by Pearson's Chi-square test or Fisher's Exact test. The significance level was determined as $p < 0.05$. In the case of Bonferoni correction, the significance level was determined as $p< 0.016$.

RESULTS

This study was performed with 441 patients presenting with ED and consulted with NSD during 2022. The median age of the patients was 57 years (IQR: 31) and 63.3% (n=279) were male.

When the presenting complaints of the patients were analysed, the most common complaint was falling with 35.6% (n=157) (Table

1). The second and third most common complaints were traffic accidents with 16.6% (n=73) and syncope with 13.8% (n=61), respectively. Regarding the methods of admission to the hospital, it was determined that 6.1% (n=27) of the patients were admitted by ambulance and the other admissions were made by the patients' own vehicles or on-foot.

Table 1. Neurosurgical consultations according to the reasons for admission.

Reason of Admission	Percentage	Count
Falling	%35.6	157
Traffic Accident	%16.6	73
Syncope	%13.8	61
Pain	%10.9	48
Seizure	%7.7	34
Assault	%2.3	10
Other	%13.2	58
Total	%100	441

It was observed that 7.5% (n=33) of the ED patients consulted with NSD did not undergo brain CT, and 19.5% (n=86) patients underwent 2 or more brain CT examinations.

When the hospitalisation status of the patients was analysed, it was observed that 53.7% (n=237) of the ED patients consulted with NSD were discharged without the need for hospitalisation (Table 2). 26.5% (n=117) patients were hospitalised in the neurosurgical service or neurosurgical intensive care unit. It was determined that 1.4% (n=6) of the patients were hospitalised in the general intensive care unit, which was monitored by anaesthesiology physicians in our hospital, and the other patients were hospitalised in different wards by different departments.

Table 2. Number and percentages of patients according to hospitalisation status.

Hospitalization Status	Percentage	Count
Externated	%53.7	237
Hospitalisation in Neurosurgical Service or Neurosurgical Intensive Care Unit	%26.5	117
Hospitalisation in General Intensive Care Unit	%1.4	6
Hospitalisation in Other Services	%18.4	81
Total	%100	441

It was observed that 12.7% (n=56) of the ED patients consulted to NSD were underwent surgery. It was found that 4.1% (n=18) of the patients consulted with NSD resulted in excitus.

No statistically significant difference was found when the patients were compared with mortality in terms of age, gender, mode of presentation and operation status (Table 3).

Table 3. Comparison of age, gender, mode of admission and surgical status data with mortality.

Parameters	Total (n=441)	Mortality		p
		No (n=423)	Yes (n=18)	
Age	57 (37-68)	57 (37-68)	63.5 (55.5-70.5)	0.076
Gender / Male	279 (%63.3)	270 (%63.8)	9 (%50)	0.172
Mode of Admission / On-Foot	414 (%93.9)	397 (%93.8)	17 (%94.4)	0.697
Surgery / Yes	56 (%12.7)	51 (%12)	5 (%27.7)	0.064

Countable data were presented as median (25th - 75th percentile) and analysed by Mann - Whitney U test. Categorical data were expressed as n (%) and analysed by chi-square test.$p < 0.05$ was accepted as a significant difference.

Patients were divided into 3 groups according to the time of presentation. Shift 1 constituted 15.6% (n=69) of all patients, shift 2 45.6%, and shift 3 38.8% (n=201). When the shift groups were compared in terms of age, gender, surgical status and mortality, no significant difference was found between the groups. However, a statistically significant difference was found between the groups in terms of ambulance or on-foot admissions to the hospital. It was determined that significantly more Neurosurgery consultations were requested during working hours ($p = 0.013$, Table 4).

Table 4. Comparison of mortality, gender, mode of admission, surgical status and age characteristics with shifting groups.

Parametreler	Shift 1 (n =69)	Shift 2 (n = 201)	Shift 3 (n = 171)	p
Mortality	2 (%2.9)	10 (%5)	6 (%3.5)	0.670
Gender / Male	41 (%59.4)	130 (%64.6)	108 (%63.1)	0.736
Mode of Admission / On-Foot	62 (%89.8)	196 (%97.5)	156 (%91.2)	**0.013**
Surgery / Yes	6 (%8.7)	31 (%15.4)	19 (%11)	0.255
Age	56 (30-66.5)	60 (43-70)	54 (31-69)	0.158

Quantifiable data were presented as median (25th - 75th percentile) and analysed by Kruskal - Wallis test. Categorical data were expressed as n (%) and analysed by chi-square test. $p < 0.016$ was considered as significant difference.

DISCUSSION

All over the world, EDs have been designed as departments where critically ill patients are admitted to the hospital, their first medical interventions are performed and their subsequent treatment is planned and they are hospitalised in the relevant departments. There are studies showing that 10-40% of the patients admitted to the ED are consulted with other departments (3-5). NSD is a department that serves a large number of patients. Patients who are in the scope of interest of the NSD have a high potential to be critically ill (8).

Traumas are still responsible for 9% of deaths worldwide. By 2030, traumas are expected to be one of the leading causes of death in the world (9). Studies have shown that patients consulted by the ED with NSD are mostly trauma patients. Traffic accidents, falls, collisions and assaults are the most common forms of trauma in studies (9,10). In our study, the most common reason for admission of patients consulted with NSD was found to be falls (35.6%), followed by traffic accidents (16.6%). Our study is similar to the literature in this respect. In our study, 63.3% of the patients were male. This may be explained by the fact that the majority of the patients consulted with NSD were trauma patients. When the literature is analysed, it is seen that males have more traffic accidents than females (11-13). Working in more dangerous jobs may also be considered to be a factor explaining the high rate of trauma and thus neurosurgical consultation in the male population.

Patients may admit to the ED by ambulance as well as coming on-foot. In studies conducted in various countries, the rate of admission by ambulance in patients admitted to the ED for any reason has been shown to be 20-30% (14,15,16,17). In another study conducted in Türkiye, the rate of presentation to the ED by ambulance was found to be 6.3% (18). Although our study was performed in a limited group of patients who were consulted to the NSD after admission, the rate of presentation by ambulance was found to be 6.1%. The result we obtained in our study is similar to other studies conducted in our country. The fact that the rate of presentation by ambulance is lower than the literature suggests that people in our region prefer to reach the ED by their own vehicles as much as possible. Detailed studies should be conducted on the accessibility and adequacy of ambulance services.

Brain CT has become an important instrument of ED practice today. It has an intensive use especially in trauma patients. Since CT examination causes radiation exposure at a non-negligible level, it should be used within appropriate indications (19). Radiation may negatively affect the health status of patients (20). In our study, it was observed that only 7.5% of the patients did not undergo brain CT and 19.5% of the patients underwent two or more brain CT scans. This shows how important brain CT examination is in neurosurgical practice.

In our study, patients were divided into 3 groups according to the time of admission. Those who admitted between 00:00 - 08:00 were grouped as shift 1, those who admitted between 08:00 - 16:00 were grouped as shift 2, and those who admitted between 16:00 - 00:00 were grouped as shift 3. It was observed that the most frequent applications were made in the shift 1 group, i.e. from morning until the afternoon. In other studies conducted in Türkiye, it was shown that the most frequent emergency department admissions were made between 16:00 - 00:00 (18,21). Although our study was conducted with a limited group of patients consulted only with the neurosurgery department, the results in terms of the hours of frequent admission are similar to other studies in our country. When the shift groups were compared with each other in terms of age, gender, surgical status and mortality, no statistically significant difference was found between the groups. A statistically significant difference was found between the shift groups in the comparison made in terms of the type of access to the ED. Patients admitted between 08:00 - 16:00 used the ambulance less. The reason for this was thought to be that it was easier to use public transport during these hours. In addition, a large number of patients are directed to the ED from the outpatient clinics that are active in the hospital during these hours, and these patients increase the on-foot admission statistics.

CONCLUSION

The majority of consultation calls from ED to NSD are for trauma patients. NSD frequently uses brain CT examination in patient evaluation. Approximately half of the patients are hospitalised as a result of the consultations. Emergency physicians can properly differentiate patients who will need neurosurgery.

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Strengthening Primary Health Care Through MOOCs (Massive Open Online Courses): A Cross-Sectional Study

ABSTRACT

Objective: After the increased number of COVID-19 positive patients, a plateau-phase and a decrease in the numbers were expected, followed by a second-phase which could lead to an increased health system workload. The importance of training well-educated and qualified healthcare professionals (HPs) has been reconsidered. The rapid spread of the epidemic revealed the limitations of traditional method education. Massive Open Online Courses (MOOCs) were offered as a solution to keep the information up-to-date and accessible. The aim of our study was to evaluate the perceptions and experiences of healthcare professionals on strengthening the health system during the COVID-19 pandemic.

Methods: In this descriptive cross-sectional multi-centered study, an online survey was applied to HPs between February-May 2021. There were 28 participating countries. Due to international participation, the survey was conducted in English.

Results: There were 88 female and 87 male participants. Most of the participants were from Europe and Euroasia. Most of them reported their income as $501-$1500 US Dollars). The duration of job experience was between 5-15 years. 111 of them have completed a postdoctoral degree.

Conclusions: According to the survey, all the groups reported as the effect of strengthening primary care by MOOCs was positive.

Keywords: Primary Care, MOOC, COVID-19.

Birinci Basamak Sağlık Hizmetlerinin MOOC'lar (Yoğunlaştırılmış Açık Kurs) Aracılığıyla Güçlendirilmesi-Kesitsel Bir Çalışma

ÖZET

Amaç: Artmış COVID-19 pozitif hasta sayısının ardından, bir plato dönemini ve sayılarda bir azalma, sağlık sistemine artan bir iş yüküne yol açabilecek ikinci bir faz tarafından takip etmesi bekleniyordu. İyi eğitimli ve nitelikli sağlık profesyonellerinin (SP'ler) yetiştirilmesinin önemi tekrar gözden geçirildi. Salgının hızla yayılması geleneksel yöntemle eğitimin sınırlılıklarını ortaya çıkardı. Kitlesel çevrimiçi kurslar (MOOC'lar), bilgiyi güncel tutmak ve erişilebilir kılmak için bir çözüm olarak sunuldu. Çalışmamızın amacı, COVID-19 pandemisi sırasında sağlık profesyonellerinin sağlık sisteminin güçlendirilmesi konusundaki algılarını ve deneyimlerini değerlendirmekti.

Gereç ve Yöntem: Bu tanımlayıcı kesitsel çok merkezli çalışmada, Şubat-Mayıs 2021 tarihleri arasında SP'lerine çevrimiçi bir anket uygulandı. Katılan 28 ülke vardı. Uluslararası katılım nedeniyle anket İngilizce olarak gerçekleştirildi.

Bulgular: 88 kadın ve 87 erkek katılımcı vardı. Katılımcıların çoğu Avrupa ve Avrasya'dandı. Onların çoğu gelirlerini 501-1500 Amerikan Doları olarak bildirdi. İş deneyimi süresi 5-15 yıl arasındaydı. 111'i doktora sonrası dereceyi tamamlamıştı.

Sonuç: Araştırmaya göre, tüm gruplar MOOC aracılığıyla birinci basamağın güçlendirilmesinin etkisinin olumlu olduğunu bildirdi.

Anahtar Kelimeler: Birinci Basamak, MOOC, COVID-19.

INTRODUCTION

A pandemic leads to significant disruption in a short span, impacting human resources, community assets, economy, and environment. While many sectors play a role in handling a pandemic, healthcare remains paramount, with a unique role in planning and response. Their primary goal is to provide timely and effective care to those affected. Every pandemic follows a trend: after identifying the first case, cases rise to a peak, plateau, and then a potential second peak. (1-4).

During fast-spreading pandemics like COVID-19, healthcare systems grapple with a surge in infectious patients and a shortage of trained workers. While hospitals usually have committees for infection control and traditional training methods such as lectures and simulations, it's extremely difficult to provide comprehensive training to all staff rapidly when facing a unique and swiftly spreading microbial threat. (1,3).

During contagious pandemics like COVID-19, physical training for medical staff is difficult due to restrictions on gatherings. Despite these challenges, it's vital for health workers to be updated on new developments. Technology, like MOOCs from global institutions, offers a solution to continue training in such scenarios. (5-8).

MOOCs, offering unlimited participation and open access, have become a significant advancement in online education. They provide video lectures, readings, and interactive forums, fostering community interactions and immediate feedback mechanisms. Although MOOCs have garnered attention in recent years, the concept predates the digital era. In the 1980s and 1990s, distance learning primarily manifested as correspondence courses. With the advent of e-learning platforms, despite initial low course completion rates, the digital shift transformed distant learning. By 2010, following this evolutionary trajectory, millions accessed renowned university courses, including Michael J. Sandel's "Justice" and Marian Diamond's "Human Anatomy". (6,9-11).

During the management of the COVID-19 Pandemic, the health sector took the most important role in preparing for this situation and providing the appropriate response. In times of the ongoing COVID-19 pandemic, meeting the health needs of the affected society and individuals should be a top priority (1). After the initial increase in patient numbers, reaching a plateau phase and a subsequent decline in numbers, another second phase was expected. Above all, the increase in the number of patients leads to a higher utilization of the healthcare system and higher workload for healthcare workers (1,2). Studies shown that the coping skills of healthcare workers increase with increasing the knowledge/training levels (3,4). The importance of raising well-trained and qualified health workers has been understood once again (1). The rapid spread of the epidemic has also shown the limitations of education by using the old methods. for this reason, intensive online courses (MOOC) have been offered as a training tool (5,6).

The aim of this research was to examine the perceptions and experiences of healthcare professionals about health system strengthening intensified online courses during the COVID-19 pandemic.

MATERIAL AND METHODS

Type of Research: This study was planned in a descriptive-cross-sectional, multi-centered research design. It was designed with core working group.

Place and Time of the Research: Research data was delivered online to health professionals working in community health and family medicine units, who accepted digital responses via e-mail. It was implemented between February and May 2021.

Questionnaire Form for Participants: This form was created by the researchers by examining the relevant literature. In general, it includes demographic data and open-ended questions.

Data Collection Methods: Data collected and sent to personal e-mails using the Google Survey program. In this study, an online survey was applied to HPs between February-May 2021. Due to international participation, the survey was conducted in English. Ethical approval was obtained from the Ethics Committee of Izmir University of Economics. Participation was based on volunteerism.

Analysis and Evaluation of Data: The data transferred to the computer environment and analyzed by using the SPSS 21.0 package program. Parametric or nonparametric analysis methods are preferred by testing number and percentage values, normal distribution and covariance compatibility for sociodemographic characteristics. Binary Logistic Regression analysis was used to evaluate the combined effects of its independent variables (strengthening PC [yes/no] and the dependent variables[promotion, Daily clinic usage, academic usage,etc]). Multinomial LR analyses were used to compare demographic data, academic degree, occupational experience duration, being in teaching position, monthly income. In the study, $p<0.05$ is accepted as a statistical significance level and the results are evaluated according to this level of significance.

Duration and Facilities: Survey questions were sent to the participants electronically between February and May 2021.

Ethical Disclosures: Written ethical permission was obtained in order to conduct the research. Among the health workers who are sent an electronic questionnaire, those who agree to participate in the study filled out the questionnaire.

RESULTS

The survey was answered by 231 participants answered the survey. When the participants were analysed for their occupation, some of them were excluded as they were not health workers and some of the participants were not answered all the questions. So in total 175 participants were analysed for the research (88 female and 87 male participants).

The countries of the participants were Albania (30), Greece (38), India (33), Kosovo (30), Romania (31), Turkey (45), United States (9), other countries(15). That's why the group of lands were classified as Europe, Middle Asia, Asia, Euroasia, America. Distribution of genders by locations are shown in Table 1 detailed.

Table 1. Distribution of genders by locations

		Number/Location					
		Europe	Euroasia	Middle Asian	Asia	America	Total
Gender	Female	47	20	6	9	6	88
	Male	42	11	8	23	3	87
Total		89	31	14	32	9	175

In general, Binary Logistic Regression analysis was used to evaluate the combined effects of its independent variables on "Demographic data", "Scientific degree", "Monthly income level", "Professional Experience", "Educational Experience", and "MOOC participation level", which can be effective on "PC Strengthening" (Dual Dependent Variable) MOOC view and perspective" (Table 2).

Table 2. Evaluation of combined effects of independent variables by binary logistic regression analysis

Categorical Variables Codings									
			Parameter coding						
		Frequency	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Income.(US dollars)	<500	5	1	0	0	0	0	0	0
	501-1000	49	0	1	0	0	0	0	0
	1001-1500	50	0	0	1	0	0	0	0
	1501-2000	21	0	0	0	1	0	0	0
	2001-2500	18	0	0	0	0	1	0	0
	2501-3000	7	0	0	0	0	0	1	0
	3001-5000	10	0	0	0	0	0	0	1
	>5000	8	0	0	0	0	0	0	0
Job.Experience	<1	4	1	0	0	0	0	0	
	1-5	37	0	1	0	0	0	0	
	>5-10	49	0	0	1	0	0	0	
	>10-15	40	0	0	0	1	0	0	
	>15-20	18	0	0	0	0	1	0	
	>20-30	8	0	0	0	0	0	1	
	>30-40	12	0	0	0	0	0	0	
Teaching.Experience	None	76	1	0	0	0			
	1-5	50	0	1	0	0			
	>5-10	28	0	0	1	0			
	>10-15	3	0	0	0	1			
	>15	11	0	0	0	0			
Homeland	Europe	87	1	0	0	0			
	Euroasia	31	0	1	0	0			
	MiddleaAsia sia	12	0	0	1	0			
	Asia	30	0	0	0	1			
	America	8	0	0	0	0			
Degree*	1	9	1	0	0				
	2	23	0	1	0				
	3	111	0	0	1				
	4	25	0	0	0				
Gender	Female	84	1						
	Male	84	0						

*Degree are: 1) Bachelors, 2) master-doctoral(student), 3) master-doctoral degree (has completed) 4) post-doctoral(carier)

The occupational status of the participants have been detailed in Table 3. Most of them answered as "MOOCs could strength the primarycare" positively (87.5%).

Table 3. Answers strengthening primary care by occupational status

			Strengthening		
			No	Yes	Total
Occupational Status	Career	Number	2	23	25
		%	8.0%	92.0%	100.0%
	PC Employee	Number	1	16	17
		%	5.9%	94.1%	100.0%
	Researcher	Number	1	4	5
		%	20.0%	80.0%	100.0%
	PC Doctor	Number	10	44	54
		%	18.5%	81.5%	100.0%
	Sp Doctor	Number	1	6	7
		%	14.3%	85.7%	100.0%
	Administer	Number	2	20	22
		%	9.1%	90,9%	100.0%
	Trainer	Number	1	21	22
		%	4.5%	95.5%	100.0%
	Asistant Doctor	Number	3	16	19
		%	15.8%	84.2%	100.0%
	Consultant	Number	1	4	5
		%	20.0%	80.0%	100.0%
Total		Number	22	154	176
		%	12.5%	87.5%	100.0%

DISCUSSION

In our study involving 231 healthcare professionals assessing perceptions and experiences related to strengthening the health system during the COVID-19 pandemic, we determined that a majority of the participants were middle-aged, with approximately half being male. We found that the majority of our participants were general practitioners having mid-level work experience, holding a master degree, and having teaching experience of less than one year (Tables 3-5). Similar finding had been observed in a study conducted by Impey C et al. It was found that the normal spring enrolment baseline of 840, the extra enrolment from March to May was 12,490. During those three months (pandemic time), 83% of all those enrolled were associated with the pandemic (7).

Majority of our participants attended more MOOCs (free of cost) during the pandemic having 3-5 sessions at the time of data collection. Among one third participants have paid 50-100 USD as MOOC fees. This may be due to the knowledge of COVID-19 was evolving and they were facing day to day challenges more than others that's why they have enrolled in the COVID -19 related MOOCs.

Another study conducted in Malaysia came to the conclusion that the 4.0 Industrial Revolution and the use of MOOC platforms for online learning were revolutionary (8). Almost all Malaysian universities have made the switch to online learning despite early reluctance, and several public universities intend to keep doing so. (9,10). The authors recommended that MOOC should be utilised as the preferred online learning platform by universities as it helps to keep the students occupied with their lessons and learning experience (6,11) .

Majority of our participants agreed that MOOC was an interesting teaching method. Similar finding was observed in previous studies (12-14).

One of the most important supplemental forms of learning (in-class learning being the primary) is through Massive Open Online Courses (MOOCs), and Jie Zhang examined how professors may better encourage students to do so. Drawing on the regulatory focus theory, the author proposed that different types of advocates (promotion-oriented or prevention-oriented advocates), to students with a different regulatory-focus (promotion-focus or prevention-focus), would yield different levels of motivation in students participating in MOOC learning. The results of the experiment suggested that proper pairing of promotion-oriented advocates with promotion-focused students and prevention-oriented advocates with prevention-focused students significantly increases students' motivation to learn from a MOOC and their assessment of the MOOC as helpful, but they typically do not produce positive evaluations from students regarding the enjoyment of MOOC learning. (15,16).

Majority of the participants got the information about MOOC from social media (17,18). It was found that MOOC courses as part of continuous medical education were significantly correlated with factors such as contribution of MOOC courses to primary care services, age, MOOC as group activity, better expression of participants and self-learning (Tables 6,7) (6,11,19,20). Along with socioeconomic differences, there may be cognitive-affective differences among all kind of students that contribute to educational inequality (21,22).

CONCLUSION

According to the survey, all the groups reported as the effect of strengthening primary care by MOOC was positive.

Recommendation: The online free course could help the primary health care workers.

Lessons for Practice section:

- In collaboration with healthcare professionals, MOOCs prove to be a valuable option for continued medical education.
- MOOCs could help with sustainable health education.
- There are differences between MOOCs in terms of assessment methods and educational quality.

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Evaluation of Risky Decision-Making and Impulsivity in Individuals with Premature Ejaculation

ABSTRACT

Objective: Different mechanisms such as psychological, neurobiological, autonomic, and genetic factors might be involved in the etiology of lifelong Premature Ejaculation (PE). Albeit cortical activity changes have been reported, the relationship between PE and impulsivity/decision-making has been minimally studied to date. The present study aimed to assess impulsivity and risky decision-making in individuals with lifelong PE for the first time.

Methods: 26 lifelong PE patients were diagnosed by the International Society for Sexual Medicine (ISSM-2014) criteria and 26 healthy volunteers were recruited. The Premature Ejaculation Diagnostic Tool, International Erectile Function Index, Barratt Impulsiveness Scale-11, Patient Health Questionnaire-9, Balloon Analogue Risk Task, and Monetary Choice Questionnaire-27 were administered.

Results: The mean age was 37. No differences were found between groups in risky decision-making and impulsivity.

Conclusions: No alterations of impulsivity and risky decision-making were found in lifelong PE patients. Impulsivity may only exist in a subset of individuals with lifelong PE or may only be evident in neural levels or specific subtypes of impulsivity.

Keywords: Decision-Making, Delay Discounting, Impulsivity, Neurophysiology, Premature Ejaculation.

Prematür Ejakülasyon Tanılı Bireylerde Karar Verme ve Dürtüselliğin Değerlendirilmesi

ÖZET

Amaç: Yaşamboyu Prematür Ejakülasyon (PE) etiyolojisinde psikolojik, nörobiyolojik, otonomik ve genetik faktörler gibi farklı mekanizmalar rol oynayabilir. Kortikal aktivite değişiklikleri bildirilmiş olsa da, PE ile dürtüsellik/karar verme arasındaki ilişki bugüne kadar çok az çalışılmıştır. Bu çalışma, yaşam boyu PE'si olan bireylerde ilk kez dürtüsellik ve riskli karar vermeyi değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Uluslararası Cinsel Tıp Derneği (ISSM-2014) kriterlerine göre 26 yaşamboyu PE hastası teşhis edildi ve 26 sağlıklı gönüllü çalışmaya alındı. Prematür Ejakülasyon Tanısal Aracı, Uluslararası Erektil Fonksiyon İndeksi, Barratt Dürtüsellik Ölçeği-11, Hasta Sağlık Anketi-9, Balon Analog Risk Görevi ve Parasal Seçim Anketi-27 uygulandı.

Bulgular: Örneklemin yaş ortalaması 37 idi. Riskli karar verme ve dürtüsellik açısından gruplar arasında fark bulunmadı.

Sonuç: Yaşam boyu PE hastalarında dürtüsellikte ve riskli karar vermede herhangi bir değişiklik bulunmadı. Dürtüsellik, yalnızca yaşamboyu PE'si olan bireylerin bir alt kümesinde mevcut olabilir veya yalnızca nöral seviyelerde veya belirli dürtüsellik alt tiplerinde belirgin olabilir.

Anahtar Kelimeler: Dürtüsellik, Karar Verme, Nörofizyoloji, Prematür Ejakülasyon, Zamansal Değersizleştirme.

INTRODUCTION

Premature Ejaculation (PE) is one of the most common sexual disorders in men that crucially affects self-esteem, subjective well-being, quality of life, quality of interpersonal relationships, and sexual satisfaction (1). Albeit various pharmacological and nonpharmacological interventions are currently available worldwide (1), there is still a requisite for therapeutic approaches directly aimed at ameliorating neurocognitive differences which have been scantily studied thus far. To this end, delineating the cognitive processes underlying the distinct subtypes of the disease may guide therapeutic interventions considerably.

The alterations of the serotonergic system were contemplated to have a more pivotal role than psychological factors in lifelong PE (2). Selective serotonin reuptake inhibitors (SSRIs) are among the most commonly used drugs to treat PE (1) which are also shown to reduce impulsiveness (3,4) and increase metabolic activity in the orbitofrontal cortices (5). To boot, serotonergic pathways in the central nervous system are involved in the regulation of impulsivity and motor behavior in general (6,7) as well as impulsive decision-making (8,9) and response inhibition processes (10,11). Moreover, abnormalities in the prefrontal and parietal cortices, which are chiefly involved in risky decision-making and impulsivity (12–14) as well as delay discounting (15,16), are indicated in individuals with lifelong PE (17). Hence, changes in impulsiveness and metabolic activity in the orbitofrontal cortices may contribute to the therapeutic effects of SSRIs in lifelong PE. Besides, a recent study reporting the potential clinical efficacy of modafinil in individuals with PE (18) also suggests a possible relationship between PE and impulsivity as modafinil has been indicated to reduce impulsivity and increase functional connectivity during impulsive decision-making (19–21). Individuals with PE also had a considerably higher incidence of adult attention deficit hyperactivity disorder (ADHD) (22,23) (especially the hyperactive and impulsive subtypes) while individuals with ADHD have also been reported to have higher rates of PE (24) which also suggests a relationship between impulsivity as ADHD is among the most common causes of impulsivity in the general population.

From a neurobehavioral point of view, impulsiveness has long been known as the choice of earlier less rewarding over late more rewarding alternatives (25) which may be tested with delay discounting paradigms (26). Delay discounting is the inability to delay receiving a lesser reward to obtain a larger reward at a later time which is also one of the widely accepted measures of impulsivity (27) and is also suggested as a part of the initial assessment of impulsivity in a systematic review (28). Even though delay discounting has not been assessed in individuals with PE before; impulsivity, novelty seeking, risk-taking, and excitement as temperament characteristics have been depicted to be higher in individuals with lifelong PE which may also point out to impulsiveness (29). Moreover, we further hypothesized that PE might also stem from an inability to delay a reward, considering the neurophysiological outputs of ejaculation as a natural rewarding behavior in males (30).

Overall, alterations of impulsivity were propounded to be evident in individuals with PE (31). However, the relationship between impulsivity and lifelong PE has not been directly tested thus far. Under the guidance of the emergent aforementioned literature, the present study aimed to assess differences in impulsivity between individuals with lifelong PE and healthy individuals. We postulated that patients with lifelong PE might have higher levels of impulsivity and altered risky decision-making.

MATERIAL AND METHODS

Setting: The present cross-sectional pilot study was conducted at Muğla Sıtkı Koçman University Faculty of Medicine. Medical examinations were performed in the Urology Outpatient Clinic and assessments of impulsivity were carried out in the Department of Physiology. Participants were selected from individuals who were admitted to the Urology Outpatient Clinic and they were referred to the Department of Physiology for further assessments if they volunteered for the present study. Participants in the control group were male patient companions of the urology service who had no urological complaints. Participants were not compensated for their time and their routine treatment was maintained.

Ethical approval was obtained from the local ethical committee (10th April 2022, decision number 26). Written informed consent was provided by all participants. All utilized procedures complied with the Declaration of Helsinki.

Participants: 26 individuals with lifelong PE and 26 healthy individuals aged between 18-55 years were recruited. An *a priori* sample size calculation was calculated using GPower 3.1.9.4 (32) with the following parameters: 2 groups, an alpha-error rate value of 0.05, the statistical power value of 0.8, and a Cohen's d value of 0.8 with regard to the effect size regarding the serotonergic challenge and impulsivity studies in a meta-analysis (33).

Individuals with lifelong PE were diagnosed as having lifelong PE by the International Society of Sexual Medicine Criteria (34) after clinical evaluation by experienced urologists. Participants were excluded if they were not sexually active or had less than four sexual intercourses in the last month as at least four Intravaginal Ejaculatory Latency Time (IELT) measurements from the last month were needed to calculate average IELT (35).

Participants without a heterosexual monogamic partner were excluded as PE diagnostic criteria for homosexual men and latency times for intercourse other than penile-vaginal intercourse have not been clearly determined yet (36). Participants that had a serious neurologic, psychiatric, or other medical illness, had a history of major pelvic/penile surgery, had retrograde/painful ejaculation or anejaculation, had a sexual partner with sexual dysfunction, or a serious medical illness. Participants who had a Body Mass Index above 40 were excluded due to the observed relationship between impulsivity and obesity (37,38) as well as conceivable cognitive changes in the obese brain (39,40). Four patients currently using phosphodiesterase inhibitors (due to a possible underdeclared erectile dysfunction risk), SSRIs, or other topical/systemic medications indicated in PE were also excluded. The lifelong PE group had a mean IELT of less than one minute in the last month, a Premature Ejaculation Diagnostic Tool (PEDT) score of more than 11, and an International Index of Erectile Function- Erectile Function subscale (IIEF-EF) score of more than 21 to exclude erectile dysfunction. Healthy individuals had a mean IELT of more than one minute in the last month, a PEDT score of less than 11, and an IIEF-EF score of more than 21 to exclude erectile dysfunction.

Procedures: General mental health status was assessed with the Patient Health Questionnaire-9 (PHQ-9) (41) while the PEDT was utilized to assess the severity of PE (42) and the IIEF-EF was utilized to evaluate the erectile function (43). Impulsivity markers consisted of the Barratt Impulsiveness Scale-11 (BIS-11) (44) and the Balloon Analogue Risk Task (BART) (45). Monetary Choice Questionnaire-27 (MCQ-27) was utilized to assess delay discounting, which was indicated to be a robust predictor of an array of behaviors related to impulsivity (26).

Measures

Patient Health Questionnaire-9 (PHQ-9): PHQ-9 is a self-report scale consisting of 9 items assessing depression levels. It originated from the PRIME-MD diagnostic instrument for common mental disorders and includes DSM-IV criteria for major depressive disorder. The interpretation of the total score is as follows: minimal/no depression (0–4), mild depression (5–9), moderate depression (10–14), or severe depression (15–21) (46).

Premature Ejaculation Diagnostic Tool (PEDT): PEDT is a 5-point Likert-type self-report diagnostic instrument consisting of 5 items (47). It is a practical tool with an approximate duration of 2 minutes which has been depicted to be a valid and reliable instrument to diagnose PE (42). Total scores between 9-10 mean probable PE while 11 or more mean definite PE.

International Index of Erectile Function-Erectile Function Subscale (IIEF-EF): The International Index of Erectile Function is a 6-point Likert-type self-report scale that consists of 5 parts as follows (43): Erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. The Erectile Function subscale (IIEF-EF) was calculated from the sum of the first five items as well as the 15th item. Its diagnostic validity is similar to laboratory tests of Erectile Function (48). An IIEF-EF total score of below 21 presumably depicts the existence of erectile dysfunction.

Monetary Choice Questionnaire-27 (MCQ-27): The MCQ-27 is a 2-choice scale consisting of 27 items which are among the most common instruments to assess delay discounting. Participants were asked to choose an early low-value or a late high-value monetary prize for each item. The main outcome measure is the k coefficient while secondary measures like proportions of consistency, and large rewards. A lower k coefficient and a higher proportion of large rewards mean lower delay discounting. On the other hand, the proportion of consistency defines the consistency throughout the test. All of them were calculated by an automated calculator (26).

Barratt Impulsiveness Scale-11 (BIS-11): Barratt Impulsiveness Scale-11 (BIS-11) is a well-established and 30-item 4-point Likert-type self-report scale that was developed to conceptualize the behavioral construct of impulsiveness (44). It was validated in a variety of diagnostic populations as well as an array of distinct cultures after 50 years of relevant research. Aside from the total score, it also has six first-order factors and three second-order factors (attentional, motor, and non-planning).

Balloon Analogue Risk Task (BART): The BART is a computerized easily administered behavioral test to assess risky decision-making. The performance of BART was considerably correlated with a myriad of real-life risk behaviors (49) as well as general risk propensity (50). Participants were told that they had 30 consequent balloons and were asked to earn money as much as they could throughout the test. Participants always had the opportunity to choose between pumping the balloon or transferring the temporary reward to the permanent account using the mouse and buttons on the screen. While up to 128 pumps were available in each balloon, there was always the risk of a random explosion. Each pump increased the temporary monetary reward from that balloon. However, participants were not able to transfer the temporary reward from a balloon in case of an explosion. The main outcome measure of the test was the adjusted average number of pumps which is the average number of pumps in unexploded balloons (45). The total number of bursts was also calculated.

Statistical Analyses: The normality of the data was assessed with Shapiro-Wilk tests. Independent Samples T-tests or Mann-Whitney *U* tests were performed to compare demographic, clinical variables, and impulsivity parameters

between individuals with lifelong PE and healthy individuals. Age, height, weight, the BART Average Adjusted Pumps (AAP), the BART number of bursts, and the BIS-11 non-planning subscale scores were normally distributed. Spearman tests were used to determine correlations between demographics, clinical variables, and impulsivity parameters.

RESULTS

Demographic and Clinical Features: Demographic, clinical features and impulsivity parameters are shown in Table 1. The mean age was 37.28 (18-55). A significant age difference was found between individuals with lifelong PE and healthy individuals (p = 0.002). The mean PEDT scores and the PHQ-9 scores of the PE patients were 9.67 and 5.69, which were higher than healthy individuals (p < 0.001). No other differences were observed between the groups. A moderate correlation between the PEDT and the PHQ-9 scores (p < 0.001; r = 0.481) was found. A weak correlation was found between the BIS-11 and the PHQ-9 scores (p = 0.038; r = 0.288).

Table 1. Differences in demographic, clinical features, and impulsivity parameters between individuals with Premature Ejaculation and healthy individuals

Variables	PE (n=26)	Healthy (n=26)	Z/t	Effect size*	*P-values*
A. Demographic and Clinical					
Age	33.23 ± 8.81	41.34 ± 8.69	3.341	0.92	**0.002**
Education (years)	12.26 ± 3.21	13.11 ± 3.39	-1.111	-0.21	0.267
Number of intercourses (Last week)	2.73 ± 1.77	1.92 ± 1.44	-1.529	-0.30	0.126
Number of intercourses (Last month)	9.38 ± 2.69	8.80 ± 3.63	-1.083	-0.21	0.279
Height (centimeters)	177.26 ± 6.98	174.30 ± 7.98	-1.424	0.39	0.161
Weight (kilograms)	84.03 ± 8.82	79.96 ± 15.19	0.917	0.32	0.376
PEDT	13.57 ± 4.90	5.76 ± 3.06	-5.145	-1.01	**<0.001**
IIEF-EF	25.53 ± 2.65	26.69 ± 2.47	-3.674	-0.72	0.148
PHQ-9	6.96 ± 1.66	4.42 ± 2.49	-0.377	-0.07	**<0.001**
B. Impulsivity parameters					
BIS-11	57.46 ± 7.46	54.88 ± 8.66	-1.149	-0.22	0.256
BIS Motor	16.73 ± 3.51	17.92 ± 3.67	-1.316	-0.25	0.188
BIS Nonplanning	25.88 ± 4.51	23.50 ± 5.18	-1.769	0.49	0.083
BIS Attentional	14.84 ± 3.83	13.46 ± 3.19	-1.158	-0.22	0.247
BART AAP	30.02 ± 15.30	28.14 ± 12.48	-0.479	0.13	0.634
BART Number of Bursts	8.96 ± 5.37	7.88 ± 4.05	-0.816	0.22	0.418
MCQ-27 k coefficient	0.07 ± 0.09	0.11 ± 0.11	-1.145	-0.22	0.252
MCQ-27 proportion of consistency	95.15 ± 4.41	95.72 ± 4.01	-0.400	-0.07	0.689
MCQ-27 PLR	31.76 ± 20.79	26.89 ± 25.56	-0.994	-0.19	0.320

*Cohen's d for Independent Samples T-Tests and r for Mann-Whitney U tests. PE: Premature Ejaculation, PEDT: Premature Ejaculation Diagnostic Tool, IIEF-EF: International Index of Erectile Function-Erectile Function, PHQ-9: Patient Health Questionnaire-9, BIS-11: Barratt Impulsiveness Scale, BART: Balloon Analogue Risk Task; AAP: Adjusted Average Pumps, MCQ-27: Monetary Choice Questionnaire-27, PLR: Proportion of Large Rewards. Significant p-values are bold.

Impulsivity Parameters: No differences were found between groups in terms of BIS-11 and its subscales, the BART number of AAP and the number of bursts, MCQ-27 *k* coefficients, proportions of consistency, and large rewards (p > 0.05).

DISCUSSION

The present cross-sectional study endeavored to assess differences in impulsivity between individuals with lifelong PE and healthy individuals with multiple determinative tools for the first time. Contrary to expectations, an alteration of impulsivity in individuals with PE was not found. Thus, the proposed relationship between PE and impulsivity was not observed. Numerous potential reasons might account for the present results. Among them, the usage of impulsiveness measures that do not exactly fit the alterations in PE and a relatively low sample size come forward.

To begin with, alterations of impulsivity might not exist in individuals with lifelong PE despite preliminary putative evidence that comes from distinct sources. Even though a higher incidence of ADHD among individuals with lifelong PE has been reported (22,23), more than half of individuals with lifelong PE still do not have ADHD comorbidity. Therefore, apparent alterations of impulsivity may be extant in a subset of individuals with lifelong PE or individuals with other types of PE.

Impulsivity is a multidimensional construct that ensues as a result of multitudinous neurophysiological and psychological factors (7). Even though widely-accepted tools scrutinizing impulsivity were utilized in the present study, other tools to assess impulsivity such as the UPPS-P Impulsive Behavior Scale that focuses on sensation-seeking and urgency (51), monetary impulsivity in real-life settings (52) or sexual discounting (53) might still be affected. Moreover, delay discounting might reflect voluntary control of behavior while PE might stem from a deficit in involuntary control of the behavior (27)**.** Alternatively, alterations of impulsivity might only be discernible at neural

levels instead of behavioral/motor impulsivity changes. Bearing this in mind, studies employing neuroimaging or electroneurophysiological techniques are required to assess this assumption.

The present study was not without limitations that should be taken into account in further relevant research. Among them, the age difference between groups and the lack of a general cognitive function appraisal come forward. Nevertheless, levels of impulsivity largely remain stable in middle-aged populations and do not differ considerably before older ages (54). Besides, the present results should not be generalized into other cultural settings despite no cultural differences have been observed in impulsivity between different cultures in some studies (55). Finally, psychological factors might also play a role in the etiology of lifelong PE, although not as much as in other types of PE (2). Although the present study sample had a low level of depressive symptoms, levels of generalized anxiety or anxiety specific to sexual performance were not observed. Future scrutiny should also evaluate anxiety or other psychological factors as possible confounders.

The present study was not able to indicate an alteration of risky decision-making and increment of impulsiveness in individuals with lifelong PE, compared to healthy individuals. Studies with larger samples from different demographic settings utilizing distinct neurophysiological assessment tools are still needed to draw firm conclusions.

Disclosure statement

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RESEARCH ARTICLE

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Turkish Adaptation and Psychometric Properties of Nıjmegen Gender Awareness in Medicine Scale: Assessment of Validity and Relıability

ABSTRACT

Objective: Gender affects how we serve and receive medical care. World Health Organization evaluates gender as a social determinant of health. However, a knowledge gap exists among physicians. The present study aims to adapt Nijmegen Gender in Medicine Awareness Scale (N-GAMS) in the Turkish language and define Turkish medical students' gender awareness level and related factors.

Methods: Two hundred seventy-two medical students participated in this cross-sectional study. The Ambivalent Sexism Inventory, Jefferson Scale of Physician Empathy- Student Version, and N-GAMS were utilized to collect data; in addition to sociodemographic form.

Results: Cronbach Alpha value for the gender sensitivity subscale of Turkish N-GAMS was calculated as 0.810, gender role ideology towards patients as 0.919, and gender role ideology towards doctors as 0.896. In the confirmatory factor analysis conducted for the scale's factor structure, the scale had a three-factor structure consisting of gender sensitivity, gender role ideology towards patients, and gender role ideology towards doctors, which are interrelated. In the criterion-related validity analysis, gender sensitivity was associated with empathy ($r=0.206$ $p=0.001$) and benevolent sexism ($r=0.148$ $p=0.015$). Gender role ideology toward patients scores was related to male gender ($t=3.920$ $p<0.001$), low empathy ($r=-0.159$ $p=0.009$), hostile sexism ($r=0.638$ $p<0.001$), and benevolent sexism ($r=0.545$ $p<0.001$). Gender role ideology towards doctors was related to male gender ($t=2.669$ $p=0.008$), low empathy ($r=-0.143$ $p=0.018$), hostile sexism ($r=0.618$ $p<0.001$), and benevolent sexism ($r=0.573$ $p<0.001$).

Conclusions: N-GAMS is valid and reliable among Turkish medical students. Turkish medical students in our sample are less gender-sensitive than their European counterparts. There is a need for education on gender awareness in medical schools.

Keywords: Gender Role, Sexism, Gender Equity, Medical Students, Medical Education.

Nijmegen Tıpta Cinsiyet Farkındalığı Ölçeğinin Türkçe Uyarlaması ve Psikometrik Özellikleri: Geçerlilik ve Güvenilirliğin Değerlendirilmesi

ÖZET

Amaç: Cinsiyet, nasıl hizmet verdiğimizi ve nasıl tıbbi bakım aldığımızı etkiler. Dünya Sağlık Örgütü, cinsiyeti sağlığın sosyal bir belirleyicisi olarak değerlendirilir. Ancak, doktorlar arasında cinsiyet konusunda yeterli farkındalık bulunmayabilir. Bu çalışma, Nijmegen Tıpta Cinsiyet Farkındalığı Ölçeği'nin (N-GAMS) Türkçe'ye uyarlanması ve Türkiye'deki tıp öğrencilerinin toplumsal cinsiyet farkındalık düzeylerinin ve ilgili faktörlerin tanımlanmasını amaçlamıştır.

Gereç ve Yöntem: İki yüz yetmiş iki tıp öğrencisi bu kesitsel çalışmaya katıldı. Veri toplamak için sosyodemografik forma ek olarak Çelişik Duygulu Cinsiyetçilik Ölçeği, Jefferson Doktor Empati Ölçeği-Öğrenci Versiyonu ve N-GAMS kullanıldı.

Bulgular: Türkçe N-GAMS'in cinsiyet duyarlılığı alt ölçeği için Cronbach Alpha değeri 0.810, hastalara yönelik cinsiyet rolü ideolojisi için 0.919, doktorlara yönelik cinsiyet rolü ideolojisi için ise 0.896 olarak hesaplanmıştır. Ölçeğin faktör yapısı için yapılan doğrulayıcı faktör analizinde ölçeğin birbiri ile ilişkili hastalara ve doktorlara yönelik cinsiyet rolü ideolojisi ve cinsiyet duyarlılığından oluşan üç faktörlü bir yapıya sahip olduğu bulunmuştur. Kriterlere bağlı geçerlilik analizinde cinsiyet duyarlılığı empati ($r=0.206$ $p=0.001$) ve korumacı cinsiyetçilikle ($r=0.148$ $p=0.015$) ilişkiliydi. Hastalara yönelik cinsiyet rolü ideolojisi puanları erkek cinsiyet ($t=3.920$ $p<0.001$), düşük empati ($r=-0.159$ $p=0.009$), düşmanca cinsiyetçilik ($r=0.638$ $p<0.001$) ve korumacı cinsiyetçilik ile ($r=0.545$ $p<0.001$); doktorlara yönelik toplumsal cinsiyet rolü ideolojisi ise erkek cinsiyet ($t=2.669$ $p=0.008$), düşük empati ($r=-0.143$ $p=0.018$), düşmanca cinsiyetçilik ($r=0.618$ $p<0.001$) ve korumacı cinsiyetçilikle ($r=0.573$ $p<0.001$) ilişkiliydi.

Sonuç: N-GAMS Türk tıp öğrencileri arasında geçerli ve güvenilirdir. Örneklemimizdeki Türk tıp öğrencileri, Avrupalı meslektaşlarına göre toplumsal cinsiyete daha az duyarlıdır. Tıp fakültelerinde toplumsal cinsiyet farkındalığı konusunda eğitime ihtiyaç vardır.

Anahtar Kelimeler: Cinsiyet Rolü, Cinsiyetçilik, Cinsiyet Eşitliği, Tıp Öğrencileri, Tıp Eğitimi.

INTRODUCTION

Sex refers to the biological differences between humans regarding reproductive functions. The term sex differences also cover physiological differences between female and male. Despite these differences existing since the beginning of time, until very soon, clinicians' knowledge of health and disease depended on males or male cells or male animals (1). This fact had detrimental effects on women's health. For example, women with heart attacks are less likely to get the proper diagnosis and treatment on time (1). Research and knowledge on sex differences are increasing in medical settings, especially on heart diseases (2), pain disorders (3), and psychiatric disorders (4).

Gender is a social construct that defines how one should behave as a woman and a man. It leads to gender norms and gender roles, which are adopted and reproduced by constituents of society (5). The gender construct is hierarchical and traditionally privileges men over women. This results in unequal power dynamics and inequality (5). In real life, it materializes as women's poverty, the gender pay gap, and violence against women and girls. The term gender differences include social components and structural inequalities of gender.

Sex and gender-based discrimination are defined as sexism. The term "sexism" was used in the 1960s first (6). Traditional sexism refers to hostility towards women. Besides, benevolent sexism is a prejudice that women need protection. These two components constitute ambivalent sexism (7). Similar to the defense mechanism "splitting," ambivalent sexist attitudes evaluate women as good or bad, black or white.

Gender affects how we serve and receive medical care, and if regarding the role in society (caregiver versus workforce), differences in perception of disease and health, healthcare access, and awareness of the rights related to health (8). In many ways, gender interacts with biology (1). Thus, World Health Organization evaluates gender as a social determinant of health (5). A recent study revealed that European internists had limited knowledge of sex and gender awareness regarding disease and health (9). A study from North Italy underlined the need for doctors to training programs on gender awareness (10). Gender-blindness lead to clinical biases, and consequantly poor quality of care (11).

Empathy is an extent that is crucial in medical practice. It includes cognition, understanding, and communication (12). Interventions based on empathy are related to less implicit bias, a mild form of discrimination (13). Morais and colleagues demonstrated that more emphatic medical students were more gender aware (14).

Verdonk and colleagues defined two attitudinal components of gender awareness in medicine as gender sensitivity and gender role ideology, depending on previous studies (15). Gender awareness means being aware of the learned behaviors of individuals, which determine differences between women and men, and the fact that is related to access and control sources (15). Gender role ideology refers to the attitudes toward patients and doctors regarding gender stereotypes (15). The construction of the Nijmegen Gender Awareness in Medicine Scale (N-GAMS) met the need for a valid and reliable scale to measure gender awareness in medical settings (15).

N-GAMS has been utilized in many countries, including Portugal (14), Switzerland (16), Spain (17), Sweden (18), Taiwan (19), and Italy (20). Akşehirli Seyfeli and colleagues studied the validity and reliability of N-GAMS in a Turkish population (21). However, they recruited a small number of participants with a specific educational level in medicine. Besides, criteria-related validity was not analyzed.

The present study aims to validate N-GAMS in a sample of medical students, including criteria-related validity, and evaluate the factors related to gender awareness among medical students.

MATERIAL AND METHODS

This is a cross-sectional study with convenience sampling method.

Participants: The present study recruited medical students of Eskişehir Osmangazi University, who are 18 years old or older, who agreed to participate in. Exclusion criteria were being younger than 18 years old or refusing to participate. Data collection was carried out between 06/01/2022 and 30/03/2022.

The researchers of the present study utilized Google Forms to send out study questionnaires. Online informed consent was obtained from all participants. The present study is approved by Eskişehir Osmangazi University Non-invasive Clinical Research Ethics Committee on 21.09.2021 with decision number 11.

Measurements: Sociodemographic data form: The authors created a form to evaluate the participant's sociodemographic properties such as age, sex, level of education of the participant and their parents, and employment status of the participant's parents.

The Ambivalent Sexism Inventory (ASI): The scale was developed by Glick and Fiske in 1996 (7). ASI aims to measure the attitudes toward gender stereotypes in two subscales. Hostile sexism (HS) and benevolent sexism (BS) subscales are 11 items each. Items use a 6-point Likert-type response scale. Lower numbers mean a more egalitarian attitude. Turkish adaptation study of the scale was conducted by Sakallı-Uğurlu (22). ASI has no reverse items.

Jefferson Scale of Physician Empathy-Student Version (JSPE): JSPE is developed to

evaluate medical students' attitudes towards empathy in a patient-physician relationship (23). The scale consists of 20 items with a 7-point Likert-type scale. Ten items are reverse-coded. Higher scores demonstrate higher empathy. Three subscales are "perspective taking," "compassionate care," and "standing in the patient's shoes." Gönüllü and Öztuna conducted the Turkish adaptation study of JSPE (12).

Nijmegen Gender Awareness in Medicine Scale (N-GAMS): Verdonk and colleagues developed N-GAMS to measure gender awareness in medical students (15). Gender awareness is conceptualized as gender sensitivity and gender role ideology in N-GAMS. Thirty-two items with a 5-point Likert style generate three subscales: "gender sensitivity (GS)," "gender role ideology toward patients (GRI-Patients)," and "gender role ideology toward doctors (GRI-Doctors)."

Adaptation Process: To conduct the present adaptation study, the authors obtained approval from Petra Verdonk, the author of the original N-GAMS study (15). Following, two independent Turkish translators with English Literature backgrounds translated from English to Turkish. The authors consulted the original scale and two translations to the mental health professionals with at least a doctoral degree. The mental health professionals were asked to compare the original items and the translations and choose one translation or make a new one for each item. The authors revised the answers and constructed Turkish N-GAMS by selecting the most voted items. Finally, the authors retranslated the scale to request final approval from Petra Verdonk.

Statistical Analysis: The authors utilized IBM SPSS Statistics 25.0 to perform statistical analysis. Categorical data are presented as frequency and percentage; continuous data are presented as mean and standard deviation. We assessed the normality assumptions of the data. Based on previous researchers the value of the items ranged to an acceptable level (24, 25, 26). The descriptive statistics of the items were presented in Table 1.

Table 1. Descriptive Statistics and Confirmatory Factor Analysis Results of N-GAMS

NGAMS	Mean	SD	Skewness	Curtosis	Corrected Item-Total Correlation	Factor Loadings 1	2	3
M2	4.27	.97	-1.580	2.367	0.378	0.33		
M3	3.34	1.44	-.405	-1.217	0.626	0.61		
M4	2.72	1.49	.219	-1.417	0.640	0.60		
M5	2.35	1.28	.644	-.677	0.566	0.56		
M6	3.30	1.20	-.252	-.852	0.521	0.47		
M7	2.45	1.41	.526	-1.079	0.561	0.49		
M8	2.86	1.26	-.077	-1.032	0.582	0.53		
M9	4.11	1.06	-.906	-.213	0.397	0.33		
M10	2.66	1.40	.234	-1.330	0.657	0.55		
M11	1.93	1.21	1.122	.083	0.496	0.43		
M12	3.23	1.28	-.283	-.989	0.701	0.64		
M14	3.81	1.12	-.821	-.004	0.559	0.49		
M15	1.40	.80	2.223	4.669	0.665		0.67	
M16	1.53	.91	1.824	2.886	0.728		0.71	
M17	1.82	1.04	.946	-.279	0.804		0.79	
M18	2.11	1.20	.778	-.501	0.798		0.78	
M19	1.95	1.18	.895	-.556	0.784		0.75	
M20	1.95	1.14	.877	-.499	0.774		0.74	
M21	2.51	1.25	.284	-1.293	0.700		0.63	
M22	2.22	1.19	.479	-1.116	0.761		0.69	
M23	1.87	1.09	1.064	.066	0.802		0.77	
M24	1.98	1.16	.871	-.445	0.781		0.77	
M25	1.94	1.00	.838	.087	0.604		0.57	
M26	1.64	1.00	1.590	1.935	0.818			0.80
M27	1.87	1.13	1.087	.091	0.798			0.71
M28	1.43	.87	2.347	5.456	0.749			0.75
M29	2.22	1.26	.521	-1.048	0.750			0.62
M30	1.54	.87	1.782	2.969	0.820			0.82
M31	1.60	1.00	1.743	2.313	0.807			0.81
M32	1.96	1.09	.883	-.222	0.799			0.73

Cronbach's Alpha levels and item-total correlation were calculated to investigate the reliability scores of N-GAMS. Besides, we performed the test-retest reliability. For construct validity, we used confirmatory factor analysis (CFA). To examine whether the factor model is identical to the original scale, we conducted alternative confirmatory factor analyses (e.g., one-factor, three-factor model) using the LISREL Package Program (version 8.80). We considered the Root Mean Square Error of Approximation (RMSEA), Comparative Fit Index (CFI), Standardized Root Mean Square Residual (SRMR), and chi-square/df to examine the adjustments of models. We run alternative models to determine the best validation of the scale. CFI should be equal to 0.90 or above (27), and RMSEA should be 0.08 or below for an acceptable fit index (28). In addition, SRMR should be equal 0.10 or below, and $\chi 2/df$ should be below 3 to get an acceptable model fit (28). Furthermore, the study examines the correlation between N-GAMS and other related measurement tools with Pearson Correlation Analysis. To examine the criteria-related validity, we conducted a t-test for demographic information such as gender.

RESULTS

The present study recruited 272 participants. Eskişehir Osmangazi University Faculty of Medicine had 1625 medical students in the data collection period. The study reached 16.7% of the targeted population.

Since N-GAMS and ASI evaluate attitudes in a gender binary philosophy, we excluded 2 participants' data who defined their sex as "other," following Rrustemi and colleagues (16). Thus statistical analysis was made with 270 participants' data. Table 2 presents the sociodemographic characteristics of the participants.

Table 2. Sociodemographic characteristics of participants (n=270)

Sociodemographic characteristics		Frequency/ Mean	Percentage/ Standard deviation
Sex	Female	154	57
	Male	116	43
Age		21.86	2.14
Grade in medical school	1	27	10
	2	26	9.6
	3	72	26.7
	4	20	7.4
	5	68	25.2
	6	57	21.1
Most stayed inhabitancy	Province center	190	70.4
	County town	66	24.4
	Village	14	5.2
Family type	Nuclear family	233	86.3
	Extended family	37	13.7
Family history of migration in the last three generations	Yes	170	63
	No	100	37
Mother's age		48.80	5.71
Mother's education	Primary	59	21.9
	Secondary	34	12.6
	High school	63	23.3
	Graduate	97	35.9
	Postgraduate	17	6.3
Mother's paid employment	Yes	108	40
	No	162	60
Father's age		53.13	6.09
Father's education	Primary	32	11.9
	Secondary	20	7.4
	High school	64	23.7
	Graduate	121	44.8
	Postgraduate	33	12.2
Father's paid employment	Yes	217	80.4
	No	53	19.6
Number of siblings	0	22	8.1
	1	131	48.5
	2	72	26.7
	3	25	9.3
	4	7	2.6
	5 or more	13	4.8
Monthly income		2896.12	3375.53

Reliability: Firstly, we examined reliability of N-GAMS. Item-total correlation of the items in the scale indicated that item 1 and item 13 were correlated with N-GAMS below 0.30, specifically, item 1: -0.142, item 13: 0.038. Thus, we excluded both items from the scale. Afterwards, the rest of 30 items of item-total correlation was varied between 0.387 and 0.820 (Table 2). The internal consistency of subscales were calculated as 0.810 for Gender sensitivity; 0.919 for Gender role ideology toward patients; and lastly 0.896 for Gender role ideology toward doctors. We have performed test and retest with four weeks interval with a small sample (n=33). Test-retest correlations of subscales were presented in Table 3.

Table 3. Pearson correlation analysis of test-retest scores of the subscales (n=33)

Subscale	Correlation coefficient	p
Gender sensitivity	0.677	<0.001
Gender role ideology-patients	0.879	<0.001
Gender role ideology-doctors	0.764	<0.001

Confirmatory Factor Analysis: Firstly, we tested the one-factor model of N-GAMS. According to the fit indices, the one-factor model showed poor adjustment ($\chi2$= 2637.75, p<0.001; RMSEA=0.143, CFI=0.90, $\chi2$/df= 6.51). As can be seen, the fit indices of the one-factor model indicated that this model was not acceptable.

Secondly, we tested a three-factor model in line with the original structure. The model fit indices revealed that the three-factor model in which all factors are interrelated was acceptable ($\chi2$=1169.26, p<0.001; RMSEA=0.084, CFI=0.95, $\chi2$/df= 2.90). However, item 9 had a lower factor loading (λ=0.29), and the correlation between gender sensitivity and gender role identity was statistically non-significant. The remaining factor loadings were significant; the range was 0.31 and 0.82. This result pointed out that gender sensitivity subscale and the subscales related to gender role ideology were not associated with each other.

Thirdly, we tested gender sensitivity and the correlation of gender role identity toward doctors and gender identity toward patients model. The adjustment of the third model was acceptable ($\chi2$=1164.75, p<0.001; RMSEA=0.084, CFI=0.95, $\chi2$/df= 2.88). Despite acceptable model fit, we examined the modification indices to improve the model. Thus, we found that some changes were statistically meaningful to improve the model's fit. We accepted the suggestions of the modification indices that set the error term freely between the related constructs following the original structure. Following these changes, the final model indicated a better adjustment ($\chi2$=1005.77, p<0.001; RMSEA=0.075, CFI=0.96, $\chi2$/df= 2.51). Factor loadings of items were statistically significant and ranged between 0.33 and 0.82 (Table 4).

Table 4. Comparison of the fit indices of the tested model

Model Fit Indices	Model 1	Model 2	Model 3	Model 4
$\chi2$ /df	6.51	2.90	2.88	2.51
RMSEA	.143	.084	.084	.075
SRMR	.12	.10	.11	.10
NNFI	.89	.94	.94	.95
CFI	.90	.95	.95	.96
GFI	.60	.78	.78	.80
AGFI	.55	.74	.74	.77
AIC	2757.75	1295.26	1286.72	1142.78
CAIC	3033.66	1584.96	1567.25	1450.87
ECVI	10.25	4.82	5.78	4.25

Notes: Model 1: One-factor model, Model 2: Three-factor model; Model 3: Three-factor model correlated Gender Role Identity towards doctor and patients, Model 4: Three-factor model with 4 correlated pairs of residuals

In a nutshell, we performed a total of four alternative models. The comparison of model fit indices of all tested models were presented in Table 4. The examination of the alternative model tests revealed that the final model which is three-factor model with four correlated pairs of residuals had better model fit indices than the remaining models (Figure 1).

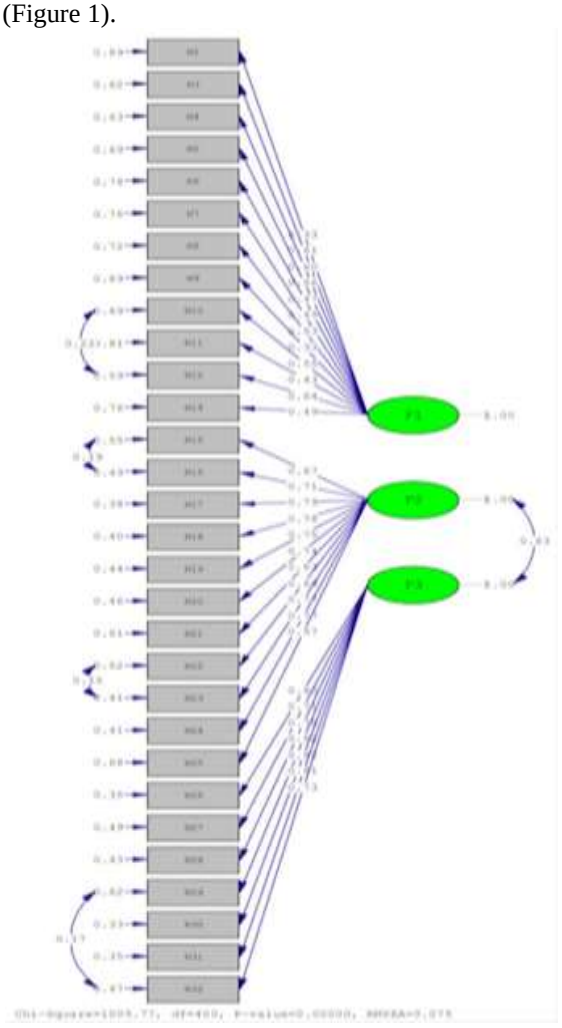

Figure 1. N-GAMS model

Criteria Related Validity: Correlation analyses were performed to assess criteria-related validity. Gender sensitivity was positively correlated with perspective taking subscale (r=0.124 p=0.042), compassionate care subscale (r=0.270 p<0.001), and the total score of the JSPE (r=0.206 p=0.001); in addition to the benevolent sexism subscale (r=0.148 p=0.015). Gender role ideology toward patients subscale scores were related to compassionate care (r=-0.277 p<0.001) and the total score of the JSPE (r=-0.159 p=0.009), together with hostile sexism (r=0.638 p<0.001) and benevolent sexism scores (r=0.545 p<0.001). Gender role ideology toward doctors subscale was correlated with the compassionate care subscale (r=-0.287 p<0.001), the standing in the patient's shoes subscale (r=-0.168 p=0.006), and the total score of the JSPE (r=-0.143 p=0.018). In addition, Gender role ideology toward doctors subscale was related to hostile sexism (r=0.618 p<0.001) and benevolent sexism (r=0.573 p<0.001). See Table 5 for an overview.

Table 5. Correlation analysis of scale scores (*:p<0.05, **:p<0.001)

	Gender sensitivity	Gender role ideology- patients	Gender role ideology-doctors
JSPE- Perspective taking	0.124*	-0.034	0.033
JSPE- Compassionate care	0.270**	-0.277**	-0.287**
JSPE- Standing in the patient's shoes	0.003	-0.071	-0.168**
JSPE- Total score	0.206**	-0.159**	-0.143**
Hostile sexism	0.097	0.638**	0.618**
Benevolent sexism	0.148*	0.545**	0.573**

Female and male medical students were compared regarding the N-GAMS subscale scores. Gender sensitivity scores did not differ between females and males (36.29 vs. 38.05, t=1.656, p=0.099). Females had lower gender role ideology toward patients subscale scores (19.41 vs. 23.75, t=3.920, p<0.001) and lower gender role ideology toward doctors subscale scores than males (11.44 vs. 13.36, t=2.669, p=0.008).

Age and grade in medical school were not correlated with any subscale scores of N-GAMS (p>0.05 each). The number of siblings was associated with gender role ideology toward patients subscale scores (r=0.196, p=0.001) and gender role ideology toward doctors subscale scores (r=0.182, p=0.003). Monthly income was not correlated with N-GAMS subscale scores (each p>0.05).

One-way ANOVA demonstrated that inhabitancy in city centers, county towns, or villages, the educational degree of the mother, and the educational degree of the father were not associated with N-GAMS subscale scores (each p>0.05). The independent sample's t-test showed that family type (nuclear family or extended family) was not related to N-GAMS subscale scores (p>0.05). N-GAMS scores did not differ if the student's family had a migration history (p>0.05). Those with employed mothers had lower scores in gender role ideology toward patients subscale (19.89 vs. 22.19, t=-2.063, p=0.040). Students whose fathers were employed had lower gender role ideology toward patients subscale scores than those with unemployed fathers (20.59 vs. 24.07, t=-2.349, p=0.022).

DISCUSSION

The present study adapted the N-GAMS scale in Turkish and assessed criteria-related validity. According to the results, the Turkish version of N-GAMS is valid and reliable.

Reliability: According to reliability findings, we excluded two items from the scale since the two had low item-total correlations. Thus, the Turkish form of N-GAMS consisted of 30 items. The subscales of Turkish form exhibited good internal consistency. In other words, the Turkish form of N-GAMS is a reliable tool for assessing gender awareness of medical students.

Confirmatory Factor Analysis: To investigate the underlying factorial structure of the scale, we performed a confirmatory factor analysis. As Verdonk and colleagues examined the construct validity with an exploratory factor analysis, we addressed this limitation and carried out an alternative underlying factorial structural model with CFA (15). Moreover, the Turkish version of this scale conducted by Akşehirli Seyfeli and colleagues' study also has some methodological limitations, including using a small sample size, carrying out EFA and CFA with the same sample, and limited adjustment of the model fit index (21). Verdonk and colleagues found that gender sensitivity and gender role ideology subscales were not correlated, whereas gender role ideology toward patients and doctors were positively associated with each other (15). Thus, we thought there might be a possible underlying factorial structure, and these two have been separate constructs. According to these findings, we performed a set of CFA models; 1) the scale has a unique factor structure, 2) the scale has a three-factor structure with each factor being correlated with the other, and 3) the scale has a three-factor structure with a separate factor for gender sensitivity, as well as two factors for gender role ideology towards doctors and patients, which are correlated with each other. Lastly, we have performed a final model with 4 correlated pairs of residuals. As a result of alternative model tests, the forth (final) model exhibited the best adjustment

following the model fit index. This is in line with the Portuguese adaptation of N-GAMS (14).

Criteria-Related Validity Analysis: Physician Empathy: Criteria-related validity analysis showed some dimensions of empathy were related to gender awareness. Compassionate care subscale scores were related to all three N-GAMS subscales. Gender sensitivity was associated with higher compassionate care subscale scores. Gender role ideology toward patients and doctors subscale scores were negatively associated with compassionate care scores. These results align with previous research (14, 29). The compassionate care dimension of empathy may be a protective factor against sexist attitudes. Thus, it may be an intervention target in healthcare education.

Perspective Taking was the other subscale of the empathy scale related to gender sensitivity. In the present study, gender sensitivity was related to higher scores in Perspective Taking. Correspondingly, in several studies, the perspective taking dimension of physician empathy was correlated positively with gender sensitivity (14, 29). We found no relation between perspective taking and gender role ideology toward patients and doctors. However, perspective taking was negatively correlated with gender role ideology subscales in the study of Morais and colleagues (14). Gattino and colleagues showed a negative correlation between perspective taking and gender role ideology toward patients (29). The difference between our study and others may be related to cultural discrepancies between countries. According to Global Gender Gap Report, Turkey ranks 124th out of 146 countries, while Portugal is 29th and Italy is 63rd (30). More common gender stereotypes may overcome the effects of perspective-taking.

Standing in the patient's shoes subscale of empathy was related to a less stereotypical approach to doctors in our study. Morais and colleagues did not calculate this subscale (14). In the study of Gattino and colleagues, standing in the patient's shoes scores were negatively related to gender role ideology toward patients and doctors scores; following the present research (29).

Ambivalent Sexism: Another result from criteria-related validity was that ambivalent sexism subscale scores correlated with gender awareness scores. Benevolent sexism was positively related to gender sensitivity and negatively associated with gender role ideology toward patients and doctors subscales. Previous studies found that benevolent sexism was correlated with gender role ideology toward patients and doctors; however, there was no relationship between gender sensitivity and benevolent sexism (14, 29).

Hostile sexism was related to higher scores of gender role ideology toward patients and doctors subscales. Morais and colleagues found similar results (14). On the other hand, Gattino and colleagues had an additional outcome; they discovered that hostile sexism correlated with gender sensitivity (29). In addition, Bert and colleagues found that increasing knowledge of gender medicine and having a sex-gender-sensitive supervisor are related to higher endorsement of gender stereotypes regarding patients and doctors (20). We know that gender sensitivity and gender role ideology are diverse dimensions of gender awareness. Gender sensitivity and hostile sexism may have an inverse parabolic relationship. High hostile sexism may result in both low and high gender sensitivity. One with a sexist attitude may value gender differences more than they should. An egalitarian healthcare worker may underestimate the differences between genders.

Medical Education Level: Grade in medical faculty did not correlate with any subscale of the N-GAMS. Diversely, Morais and colleagues found a weak but significant correlation between years of medical education and gender awareness, showing gender awareness rises after medical education (14). A study from Turkey reflected the need for gender awareness in medical faculties: 77.8% of the 6th-grade medical students found internal medicine as the most suitable specialty for female doctors (31). Altınöz and colleagues indicated that there are no differences in terms of attitudes toward gender roles between 1st-grade and 6th-grade medical students in the same faculty (32). A similar need of medical students for training on gender was identified in the study of Andersson and colleagues (33). Gender, hence gender bias, is embedded in culture and tradition. While growing up, the members of society absorb the gender stereotypes they observe. Gender stereotypes are presented in television, cinema, song lyrics, showcases, and everywhere. Medical students come to the medical faculty with this luggage. Thus medical faculties should include training against gender bias. Being a physician comes with great responsibility. Treating patients differently without a scientific reason is not acceptable. Gender bias harms healthcare, it should be extinguished.

Sex Differences: In the present study, female and male students were not different regarding gender sensitivity. But females had lower scores of gender role ideology toward patients and doctors. Particular research demonstrated similar results (14, 15). On the contrary, a study with Italian medical students found that females had higher gender sensitivity, and gender role ideology toward doctors scores were not different between sexes (20). But still, male medical students had higher scores of gender role ideology toward doctors (20). In a Swiss sample, female and male medical students were not different regarding gender sensitivity and gender role ideology toward doctors; however, males had higher scores of gender role ideology toward patients (16). A comparative study of Dutch and Swedish first-year medical students revealed that male medical

students endorsed a more stereotypical attitude toward patients than their female counterparts (18). Eventually, one may conclude that female medical students have an advantage regarding gender awareness, and sometimes they are equalized with males. Female medical students may face difficulties being young women; thus, they may be more aware of gender in general. Male medical students should be a prioritized target for gender-focused training.

Number of Siblings: The number of siblings of the medical student was associated with gender role ideology toward patients and doctors subscale scores. Patriarchal culture is known to incite having children. This relationship may depend on being raised in a sexist environment and internalizing sexist attitudes.

Comparision of N-GAMS Scores of Medical Students Between Countries: Comparing gender awanereness scores of Turkish medical students and medical students from other countries; we observed some discrepancies: the medical students in our sample had lesser gender sensitivity than other studies (14-16, 18, 20). Gender role ideology scores of Turkish medical students were similar to their counterparts from other countries. We may conclude that Turkish medical students need training on gender sensitivity.

Limitations and Strengths: The present study had several limitations. First, the study suffered from significant attrition. It could reach 16.7% of the targeted population. Second, the present study is cross-sectional, thus unable to present causality.

The strengths of the present study are performing criteria-related validity and examining the underlying factor structure of the N-GAMS.

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