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From the Editor

Dear readers,

In the third issue of 2022, we have prepared 14 research articles that we think will be interesting for you. We hope that these articles will be a guide for healthcare professionals, especially primary care physicians.

We are proud that our journal has the highest citation rate among the primary care journals published in Turkey. Thank you for your growing interest in our journal.

Please stay tuned for the next issue.

Assoc. Prof. Dr. Ahmet Keskin

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Research Article

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HOW RUSSIAN-UKRAINIAN WAR CHANGED THE USAGE OF TELEMEDICINE: A QUESTIONNAIRE-BASED STUDY IN UKRAINE

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Abstract

Objectives: Russian military aggression caused the biggest crisis in Ukraine since WWII. Telemedicine could become a solution for Ukrainian healthcare to cope with these challenges, considering previous experience and available resources. We aimed to assess features of telemedicine in Ukrainian during the war.

Materials and Methods: We used a cross-sectional approach to receive feedback from 125 Ukrainian medical practitioners performing clinical practice in Ukraine during the war. E-questionnaire was distributed among doctors via social media announcements, specific doctors' associations in messengers and direct messages.

Results: We found that 99.20% of doctors (n=124) continued using telemedicine during the war. 56.80% of the respondents (n=71) highlighted that the war resulted in the acceleration of telemedicine usage. The most popular telehealth services were instant messaging apps (97.60% of doctors, n=122) and phone calls (84.80% of doctors (n=106). Compared to less experienced colleagues, medical practitioners with more than 10 years of clinical practice more intensively used e-mail (46.15% vs 19.18%; χ^2=10.444, p=0.001), SMS (34.62% vs 15.07%; χ2=6.512, p=0.011), remote pulse oximetry (19.23% vs 5.48%; χ2=5.774, p=0.016), blood glucose monitoring (11.54% vs 2.74%; χ2=3.925, p=0.048). The main restriction of using telemedicine was an inability to perform an effective objective examination.

Conclusion: Our research showed that the ongoing Russian-Ukrainian war had accelerated the use of telemedicine by Ukrainian medical practitioners. The most common telemedical services were messengers and direct phone calls. Experienced doctors more frequently used e-mail, SMS and devices for remote patient monitoring.

Keywords: Telemedicine, Russian-Ukrainian war, wearables.

Introduction

The biggest humanitarian crisis in Europe since the Second World War is currently developing in Ukraine due to eight years of Russian military aggression with the new powerful impulse initiated by the large-scale war on 24 February 2022. As a result, after five months of the war, 6.3 million Ukrainians remain internally displaced and 5.8 million across Europe. Millions of people in the temporarily occupied territories and regions with intense hostilities faced difficulty accessing medicines and healthcare.[1]

The Ukrainian healthcare system, which was previously affected by the COVID-19 pandemic, faced several challenges in providing appropriate health care to all citizens. Firstly, most internally displaced persons (IDPs) stayed in the Western and Central Ukrainian regions like the Vinnytsia Oblast. It caused increasing pressure on the health care infrastructure in that territory. At the same time, health facilities in the regions under hostilities regularly experience attacks by the Russian army. World Health Organization (WHO) has already officially verified 390 attacks on health care infrastructure and transport in Ukraine that caused injuring and killing of healthcare staff.[2] Health care facilities in the occupied territories have been cut off from the supply of medications, medical oxygen, equipment and consumables and cannot transport patients who need more intensive care. Additionally, the Ukrainian economy is deeply affected by military actions, the inability to use seaports to export commodities, and regular missile air strikes on the infrastructure of the whole territory with human casualties. The World Bank estimates that Ukraine's economy will shrink by 45.1% in 2022 but could become more devastating depending on the duration and intensity of the Russian invasion.[3]

Active usage of telemedicine could become a solution for Ukrainian healthcare to cope with all these challenges considering that telemedicine could provide cost-effective, accessible care and clinical services for a vulnerable population living in different locations, including remote areas with limited access to healthcare facilities. Traditional telehealth services include video visits, telephone calls, secure messaging and remote patient monitoring using wearables.[4] Healthcare & Public Health Sector Coordinating Councils, additionally to the clinician-to-patient category of telehealth services, also highlight the importance of clinician-to-clinician services that includes communication between clinicians to share clinical information and discuss patient care, telementoring and training.[5]

In 2016 Ukraine made a step forward in the adoption of telemedicine, realizing the project "Support Reforms and Good Governance in the Health System in Ukraine" by the Government of Ukraine with the collaboration of the World Bank and the Swiss Development Cooperation Office in Ukraine.[6] Starting in 2019, regional telemedicine centers were opened in major cities all over Ukraine to provide telemedicine clinician-to-clinician consultations.[4]

Ukraine has a great prerequisite for broader implementation of telehealth services because of the availability of Internet access (more than 75% of the population used the Internet in 2020), widespread mobile cellular access (129 mobile cellular subscriptions per 100 people in 2020), the broad rollout of third-generation (3G) and fourth-generation (4G) networks in rural areas and including telemedicine in the Program of Medical Guarantees that allows it to be reimbursed by National Health Service of Ukraine.[4,7] Moreover, the 2020 United Nations Development Program (UNDP) survey showed that 53% of the responding Ukrainians obtained at least one e-government service in the last 12 months. Respondents chose medical services as the sector most important to have additional or better electronic services.[8]

Before the war, the Ukrainian healthcare system had advancements in developing telemedical services in several fields, including cardiology,[9,10] pulmonology,[11-13] otolaryngology,[14,15] oncology,[16] and rehabilitative medicine.[17,18]

Unfortunately, there is no current data presenting the influence of war on how medical practitioners in Ukraine use telemedical services. Moreover, there is no recent research on the preferred telemedical services by medical doctors in Ukraine, which makes the estimation of the current situation and perspectives on using telemedicine unclear. We aim to investigate how the ongoing Russian-Ukrainian war changes the usage of telemedicine by Ukrainian medical practitioners and to define what telehealth services are used during the war.

Materials and Methods

We assessed features of telemedicine in Ukraine by applying a cross-sectional approach. The sample size of this research reached 125 Ukrainian medical practitioners.

The inclusion criteria for participants of this study consisted of the willingness to become respondents, signed informed consent, and appropriate digital literacy to fill the e-questionnaire. Moreover, respondents have to confirm that they have a valid medical license to perform medical practice in Ukraine and are currently working as medical doctors in Ukraine during the war.

Our team created the Google form e-questionnaire to assess telehealth services used by medical practitioners and the change in telemedicine use during the Russian-Ukrainian war. The Google form was distributed among Ukrainian medical practitioners through several channels of communication: via social media announcements (Facebook, Twitter, Instagram), via specific physicians' associations in messengers (Viber group of young scientists of National Pirogov Memorial Medical University, Vinnytsya with more than 150 members, Viber group of the Podillia Association of medical doctors with over 300 members, Viber group dedicated to

postgraduate education of medical doctors with over 3000 members) and by the direct messages to clinicians from the database of the research team based on a previous collaboration initiative (WhatsApp, Viber, Telegram or e-mail).

Questionnaire description

This questionnaire was designed in Ukrainian. It included ten questions. The clinicians should choose their specialization, work experience, and percentage of their clinical work done using telemedicine and indicate whether usage of telemedicine was increased, decreased or not changed after the Russian large-scale military invasion. The scope of telemedicine used was another question for understanding whether the doctors used it for clinician-to-patient communications, clinician-to-clinician communications or both. Clinicians were asked to define what telehealth services they use with a separate question to investigate how they use messenger applications. Participants were asked about the technical solutions used for telemedicine and to tell about their points of dissatisfaction with telemedicine. It was obligatory to provide the informed consent of the survey participant to complete the questionnaire, with the statement that the participant has a valid medical license to perform medical practice in Ukraine. Participation was anonymous.

The study was conducted during the active military Russian invasion of Ukraine, from mid-April to mid-July 2022.

Statistical analysis was performed using IBM SPSS Statistics version 26.0. Descriptive statistics were used in our research. All continuous variables were presented with mean ± standard deviation (SD). The Pearson chi-square test was used to compare categorical variables between the groups of medical doctors with various clinical experiences. P-values <0.05 were considered to be statistically significant.

Results

We received responses from 125 Ukrainian medical practitioners, most of whom were internists and general practitioners (GP). However, 18 different medical specialties were represented in the questionnaire (Figure 1).

Participants of our research were equally distributed based on their clinical experience: 51 (40.80%) medical practitioners had less than five years of clinical experience, 22 (17.60%) had from 5 to 10 years of clinical experience, and 52 (41.60%) were the most experienced with more than ten years of clinical work.

Most medical doctors (n=124, 99.20%) continued using telemedicine in their practice in Ukraine during the ongoing war (figure 2). Only one clinician did not use any telemedical solutions in practice. Almost 70% of medical practitioners (n=86) reported that 1% to 30% of their clinical visits were performed via telemedicine.

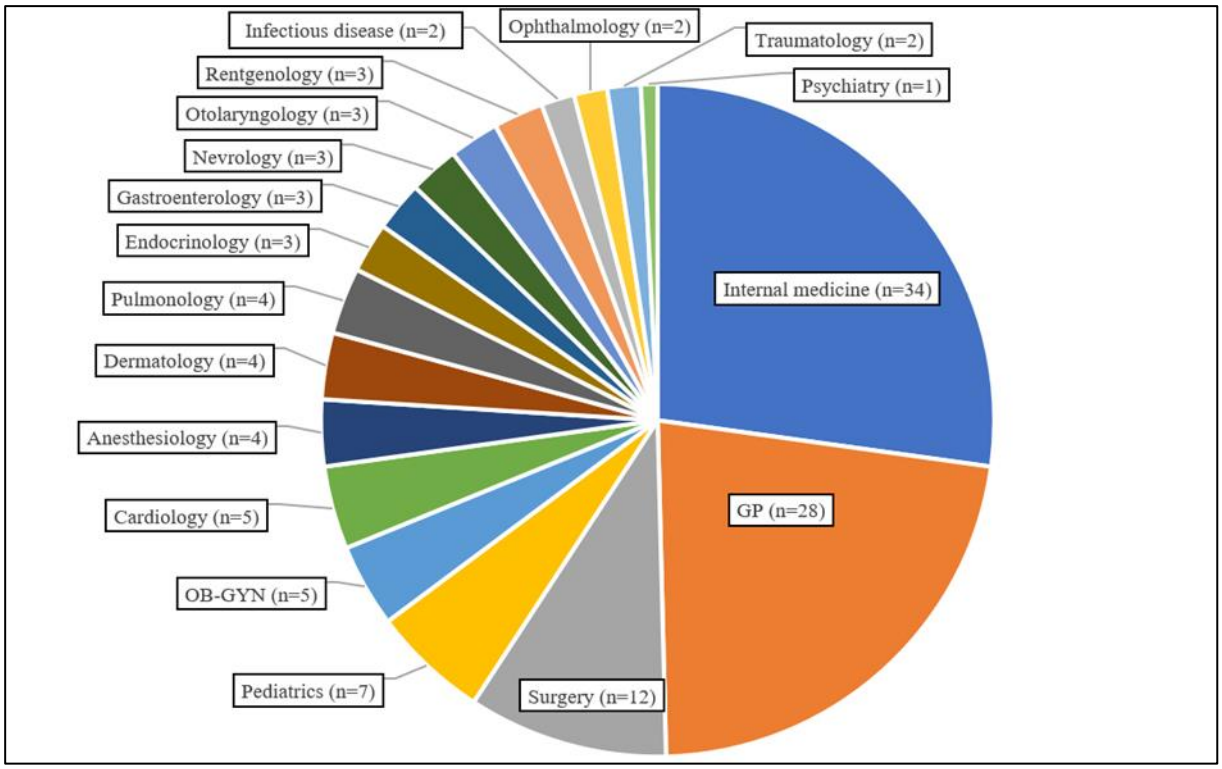

Figure 1. Structure of medical specialties presented in the research (OB-GYN: Obstetrics and Gynecology GP: General Practitioner)

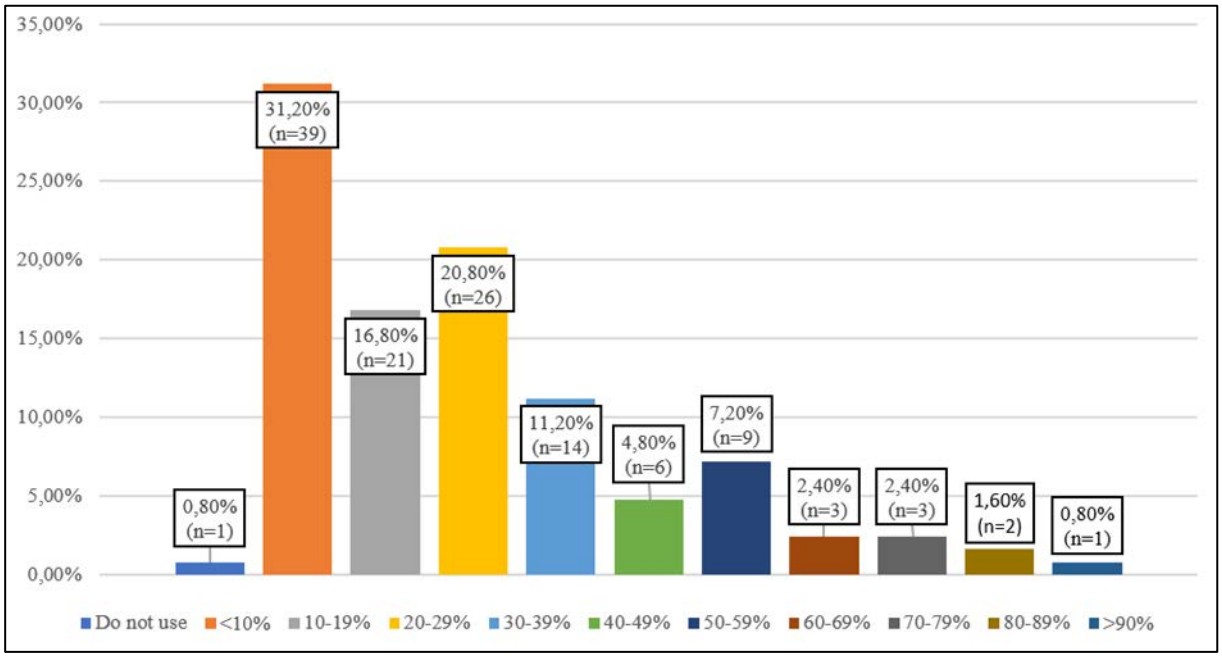

Figure 2. Percentage of telemedicine in clinical workflow during the war

At the same time, most respondents highlighted that the ongoing war resulted in the accelerating of telemedicine use by them (n=71, 56.80%) and 46 (36.80%) doctors noted that war did not influence their use of telemedicine. Only 8 (6.40%) medical doctors reported a reduction in telemedicine. Using both clinician-to-patient and clinician-to-clinician telemedicine services was reported by 97 (77.60%) respondents. Seventeen (13.60%) medical practitioners used telemedicine only for clinician-to-patient services, and ten responders (8%) used only the clinician-to-clinician category.

Only ten responders (8%) used the official software platforms for telemedicine (Figure 3). Others used unofficial services to interchange information both with colleagues and patients. Among these solutions, the most popular was using instant messaging apps (Viber, Telegram, WhatsApp) reported by 122 (97.60%) medical practitioners. These apps were used to exchange text messages in 86.40% of cases (n=108), exchange photos or video messages in 77.60% of cases (n=97), as a platform for video meetings in 38.40% of cases (n=48) and exchange audio messages in 30.40% of cases (n=38). The second most common way of communication was a phone call to the patient or colleague, which was highlighted by 106 (84.80%) doctors. Every third medical practitioner used e-mails or video meeting apps (Zoom, Skype, Google Meet, Microsoft Teams) as a telemedical solution, and every fourth doctor used Short Message Service (SMS).

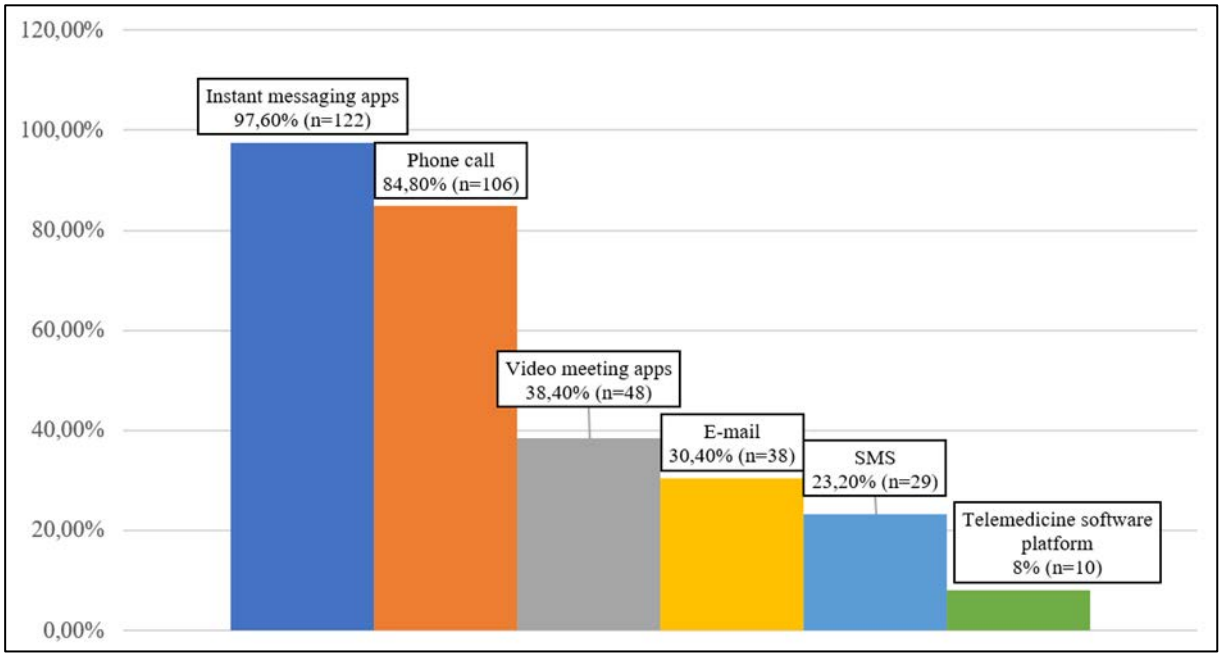

Figure 3. Telehealth services used for telemedicine

Instant messaging apps and phone calls were the most common types of services used by medical practitioners with various clinical experiences (Table 1). However, doctors with more than ten years of clinical experience showed higher usage of e-mail and SMS compared to their less experienced colleagues (46.15% vs. 19.18%; $\chi2=10.444$, $p=0.001$) and 34.62% vs. 15.07%; $\chi2=6.512$, $p=0.011$). Moreover, more experienced clinicians used instant messaging apps more often for video meetings (53.85% vs. 27.40%; $\chi2=8.981$, $p=0.003$), with no significant difference in other ways of its use (exchange of text, photo, video or audio messages).

Table 1. Distribution of telehealth services based on the clinical experience of medical practitioners

	≤10 years of clinical experience (n=73)	>10 years of clinical experience (n=52)	P-value
Instant messaging apps	97.26% (n=71)	98.08% (n=51)	0.769
• text messages	87.67% (n=64)	84.62% (n=44)	0.623
• photo/video messages	78.08% (n=57)	76.92% (n=40)	0.878
• video meetings	27.40% (n=20)	53.85% (n=28)	0.003*
• audio messages	30.14% (n=22)	30.77% (n=16)	0.940
Phone call	86.30% (n=63)	82.69% (n=43)	0.580
Video meeting apps	34.25% (n=25)	44.23% (n=23)	0.258
E-mail	19.18% (n=14)	46.15% (n=24)	0.001*
SMS	15.07% (n=11)	34.62% (n=18)	0.011*
Telemedicine software platform	9.59% (n=7)	5.77% (n=3)	0.438

The smartphone was the most popular technology solution for telemedical purposes. It was used by 117 (93.60%) of our respondents (Figure 4). More than half of medical doctors (56.80% (n=71)) used laptops. For remote patient monitoring, the wearable finger pulse oximeter was used by 14 doctors (11.20%), the blood glucose monitor by eight doctors (6.40%), the peak flow meter and the spirometer by one doctor (0.80%).

We found out that more experienced doctors more intensively used solutions for remote patient monitoring compared to their less experienced colleagues: statistically higher usage of the pulse oximeter (19.23% vs. 5.48%; $\chi2=5.774$, $p=0.016$) and blood glucose monitor (11.54% vs. 2.74%; $\chi2=3.925$, $p=0.048$) (Table 2).

During our research, we received feedback from 37 medical practitioners based on their points of dissatisfaction with the adoption of telehealth in the Ukrainian health care system. The main restriction of using telemedicine was an inability to perform an effective objective examination of the patients, and this limitation was pointed out by 21 respondents (16.80%). Six respondents highlighted an unstable internet connection during telemedical communication as the most critical restriction (4.80%). Imperfect payment systems and legislation issues for telemedical services were highlighted as the main issues by five medical doctors (4%), and low health and digital literacy among patients by another five doctors (4%).

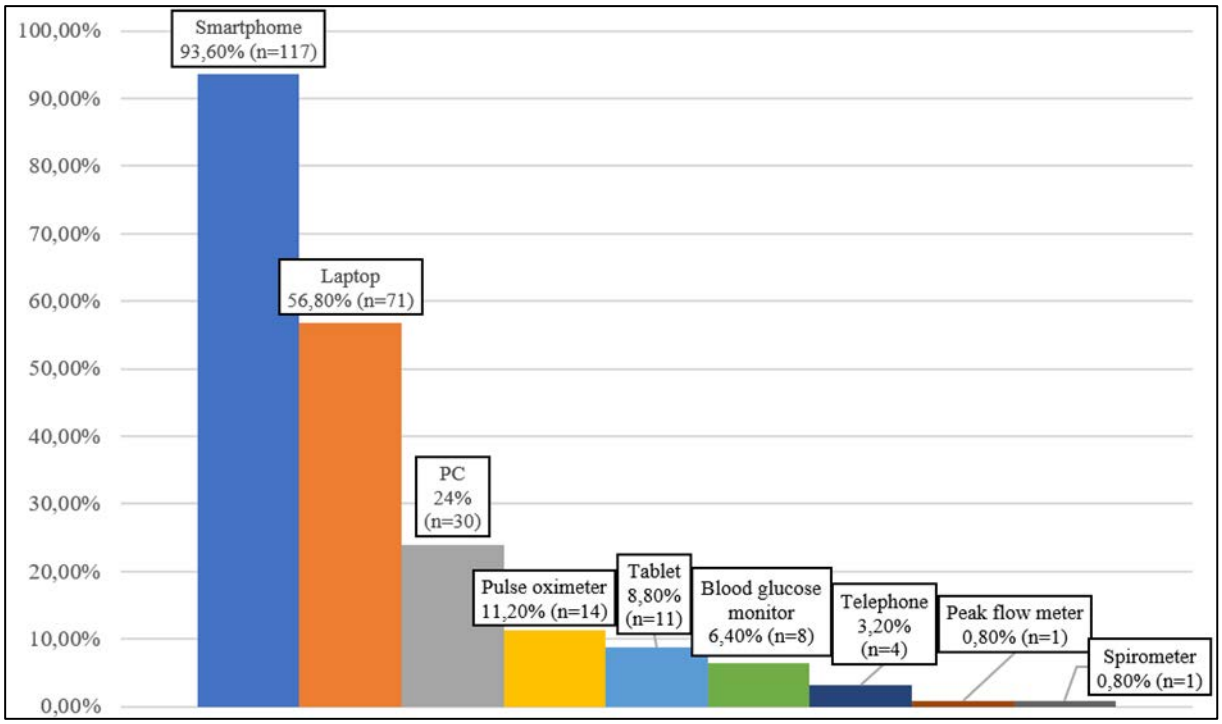

Figure 4. Technical solutions used for telemedicine (PC: Personal Computer)

Table 2. Distribution of technical solutions based on the clinical experience of medical practitioners

	≤10 years of clinical experience (n=73)	>10 years of clinical experience (n=52)	P-value
Smartphone	94.52% (n=69)	92.31% (n=48)	0.618
Laptop	58.90% (n=43)	53.85% (n=28)	0.574
PC	21.92% (n=16)	26.92% (n=14)	0.518
Pulse oximeter	5.48% (n=4)	19.23% (n=10)	0.016*
Tablet	9.59% (n=7)	7.69% (n=4)	0.712
Blood glucose monitor	2.74% (n=2)	11.54% (n=6)	0.048*
Telephone	2.74% (n=2)	3.85% (n=2)	0.729
Peak flow meter	-	1.92% (n=1)	0.234
Portable spirometer	-	1.92% (n=1)	0.234

*Statistically significant

Discussion

To the best of our knowledge, this is the first study showing that the ongoing Russian-Ukrainian war increased the intensity of using telemedicine for most respondents, compared to doctors who reported that war had no influence on telemedicine usage or resulted in a decrease in it accordingly. These changes in using telemedicine were also stimulated by the Ministry of Health of Ukraine, which launched access to a free medical consultation through the contact center of the Ministry of Health for all Ukrainians during martial law in Ukraine.[19]

Syrian cardiologists had recently presented a similar tendency in using telemedicine during the war; when this country's healthcare system was faced with destroyed or seriously damaged health facilities, millions of displaced citizens and physicians fled the country. In such circumstances, telecardiology helped alleviate some of this disastrous shortage in health care coverage for patients with cardiovascular diseases.[20]

Perspectives and the importance of using telemedicine to respond appropriately to such manufactured disasters as the war was already highlighted in the North Atlantic Treaty Organization (NATO) development, a Multinational Telemedicine System (MnTS) for disaster response. This system was tested in Euro-Atlantic Disaster Response Coordination Centre's (EADRCC) Exercises Ukraine 2015 showed that using an integrated system focused on Web-based tools showed that it could provide citizens with appropriate medical care much more effective than traditional methods.[21]

Almost all medical practitioners who participated in our survey reported that they used telemedicine in their clinical practice in Ukraine during the ongoing war, which was unexpectedly high. Most respondents reported that about one-third of the clinical workflow was done by telemedicine. Since there are no specific statistics on the exact number of Ukrainian doctors using telemedicine in their practice, our research provides unique data. It happened because Ukrainian medical doctors and their patients used messengers and direct telephone calls for telemedical purposes that could not be officially registered and covered by the National Health Center of Ukraine or insurance companies. However, before the COVID-19 pandemic during the previous five years, the telemedical market in Ukraine demonstrated 46% growth, with further advancements during the pandemic period presenting positive background for the current active use of telemedicine. As of October 2021, there were officially registered 26 Ukrainian telehealth providers. One of the largest professional telemedicine networks in Ukraine – Medinet, reported that over 4 500 doctors from 624 medical institutions provided 18 000 teleconsultations using their platform by April 2021.[4]

It is impossible to compare our results with other countries experienced in military countries because the current Russian-Ukrainian war is the most significant military conflict in Europe since the Second World War. It is the largest war in a developed country with telemedical services. That is why we compared our results with data from other countries during the COVID-19 pandemic and noticed that our data are representable and highlight the high level of adoption of telemedicine in Ukraine despite the ongoing war. According to data from the Centers for Medicare and Medicaid Services (US), during the COVID-19 pandemic use of telemedicine greatly depended on medical specialty varying from 68% of clinical visits for endocrinologists to 9% - for ophthalmologists. From January to June 2020, about one-third of all visits were provided via telemedicine, which is quite similar to current data from Ukraine, where most physicians reported the same amount of visits provided via telemedicine[22]. Our data correlate with another data published by a UK-wide National Health Service (NHS) survey aimed to assess video consulting across England, Northern Ireland, Scotland and Wales

from January 2020 to August 2021. The reported proportion of video consultations during the first six months of the COVID-19 pandemic was the highest in Scotland (45%) and the lowest in Wales (25%).[23] Moreover, according to the British Medical Association, 65.13% of GPs provided remote consultations for their patients in May 2020 compared to 93.70% of Ukrainian GPs in our survey during the current war and pandemic.[24]

Notably, almost all our respondents did not use official software platforms for telemedicine but preferred using other services like instant messaging apps (Viber, Telegram, WhatsApp). The reason for this tendency includes inaccessibility to official telemedicine software platforms that had just started developing in Ukraine before the war and the disorganization of healthcare during the first months of the war. Data reported from Syria during the ongoing Syrian conflict also state that in the case of the military situation, physicians prefer using low-cost solutions to share and receive data from patients or colleagues. Syrian cardiologists used social media platforms and apps to provide care to their patients.[20] However, using unofficial technical platforms and solutions for telemedicine raises data privacy concerns. Unfortunately, Ukraine is not subject to the European Union (EU) General Data Protection Regulation that could guarantee the safety of personal data through the verified application. However, in 2021 Ukraine has registered Law Draft "On Personal Data Protection", following obligations under the EU Association Agreement that is expected to become effective in 2023.[25]

Our respondents considered the inability to objectively examine patients during teleconsultation as the most significant barrier to implementing telemedicine, with further emphasis on legislation issues, remuneration plans, connection issues, data transfer and low literacy among patients. These results are quite typical, and the usual barriers to telemedicine implementation worldwide are presented in the vast majority of previous research.[26] In the research performed in China among physicians during the COVID-19 pandemic, respondents also highlighted the inability to examine patients in person as the most significant barrier to telemedicine usage.[27] The same as in our research, Chinese physicians pointed out that, for better promotion of telemedicine, it is crucial to develop performance measures, including monetary incentives and improved policy support.

Our study has several limitations. First, our research included only medical practitioners with a high-level digital literacy, allowing them to fill the e-questionnaire while making these persons more susceptible to digital technologies in their clinical practice. Moreover, our study could not be scaled to the county level because we received data from clinicians, mostly from Vinnytsia Oblast. However, we consider the Vinnytsia Oblast representative on the national scale because it is one of the largest central regions of Ukraine, which became a new home for many citizens running from the war. Almost 170000 IDPs are officially registered in the Vinnytsia Oblast, including almost 1500 people with disabilities, which caused an increase in the regional population to more than 10%.[28] Health care system of this region provides care for previous residents, IDPs and wounded soldiers under the economic issues, restrictions of martial law and Russian missile attacks.[29]

In conclusion, our results show that the ongoing Russian-Ukrainian war has accelerated the use of telemedicine by Ukrainian medical practitioners as a solution to provide quality care for patients even at the frontline. Medical doctors in Ukraine used various telemedical services with messengers and direct phone calls forming the predominant part of the workflow. Experienced medical doctors more frequently used e-mail, SMS and devices for remote patient monitoring compared to their less experienced colleagues.

Ethical Considerations: The research does not require ethical approval, considering anonymous data collection without information about participants' health status or other sensitive topics.

Conflict of Interest: The authors declared no potential conflicts of interest concerning this article's research, authorship, and/or publication.

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Research Article

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PREVALENCE OF SEXUAL DYSFUNCTIONS IN MEN AGED 18-65 AND RELATED FACTORS: A META-ANALYSIS AND META-REGRESSION STUDY FROM TURKEY

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Abstract

Objectives: Studies on male sexual dysfunctions around the world point to high prevalence rates. Although there are studies on the prevalence of sexual dysfunctions in men in Turkey, these studies report different results due to regional and methodological differences. Therefore, more robust and consolidated data are needed on the prevalence of sexual dysfunctions in men.

Materials and Methods: For this meta-analysis study, "Google Scholar" and "ULAKBIM" databases were searched. Studies have been conducted in Turkey between January 2000 and April 2019 were included in the study.

Results: The prevalence of male sexual dysfunction, erectile dysfunction and premature ejaculation were found to be 28%, 18% and 24%, respectively.

Conclusion: This study is the first meta-analysis on the prevalence of male sexual dysfunction in Turkey. Our results reveal the importance of preventive and therapeutic health services in male sexual dysfunctions.

Keywords: Erectile dysfunction, men, meta-analysis, premature ejaculation, sexual dysfunction.

Introduction

Loss of function in one or more stages of sexual psychophysiology, such as interest/desire, arousal, orgasm, and resolution, is defined as sexual dysfunction.[1,2] According to the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM 5), although sexual dysfunctions are handled in different categories, they are intertwined to different degrees.[3,4] Erectile dysfunction (ED) and premature ejaculation (PE) are the most common male sexual dysfunctions. ED is the inability to achieve and maintain an adequate erection to allow satisfactory sexual performance.[5] PE is characterized by ejaculation that always or nearly always occurs before or within about one minute of vaginal penetration, the inability to delay ejaculation on all or nearly all vaginal penetrations and negative personal consequences such as distress, bother, frustration and the avoidance of sexual intimacy.[6] Although the prevalence of ED and PE varies in studies, it is estimated that 5-20 and about 30%, respectively. This variability is probably due to study methodologies, sample age, and sociocultural factors.[7-9]

Sexual health can be sustained by the interaction of many biopsychosocial components. Although sexual life is primarily handled from a physiological point of view, it is also under the control of cognitive and emotional factors and is affected not only by the presence of medical conditions but also by psychosocial conditions. While sexual health is affected by these factors, it is also in a position to affect these factors. In other words, healthy sexual life is also necessary for maintaining physiological and psychosocial health. The role of sexual health in terms of general health and quality of life cannot be ignored, and the protection of sexual health should be at the forefront of public health services.[10]

Although more has been studied in women, there are relatively few studies on the epidemiology of male sexual dysfunctions (MSD).[6] The studies on MSD are mostly regional and there is a risk of bias for MSD, which can be affected by a large number of demographic, geographical, and cultural factors. Therefore, a meta-analysis study on the prevalence of male sexual dysfunction can provide the consolidation of the findings of these regional studies. The secondary objectives of this study are to create data for public health policies for male sexual dysfunctions. In addition, the high prevalence rates of male sexual dysfunctions may, in some ways, indicate the inadequacy of both the provision of appropriate treatments and access to these treatments. It, therefore, emphasizes the need to improve and expand existing MSD treatment offerings.

Materials and Methods

Search Strategy

The methods for this meta-analysis were developed according to recommendations from the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statements.[11] Scans for the meta-analysis study were carried out using "Google Scholar" and "ULAKBIM TR Directory" databases. The search words were as in English it was as follows; "sexual function", OR "sexual problem", OR "sexual dysfunction", OR "erectile dysfunction", OR “erectile”, OR "premature ejaculation", AND Year: 2000 - 2019, OR Database: Science, OR Database: Social. The reasons for choosing these databases; Google scholar has an extensive database for a large number of research papers carried out in Turkey. ULAKBIM includes national articles.

The literature search and review were carried out by the researchers. All abstract and title sections have been revised according to their relevance to the meta-analysis. Suspicious articles were included until the full text was examined. The final inclusion of the studies was achieved through the review of two separate researchers. In case of conflict, a third researcher examined the article and made the decision. If different articles originate from a single study, the most recent of them were included. A second screening was made by examining the reference part of the final articles (Figure 1).

Eligibility Criteria

The study included a meta-analysis that reported the rates of any MSD in healthy male volunteers between January 2000 and April 2019, or at least one sexual dysfunction (such as erectile dysfunction or premature ejaculation). Observational studies such as cross-sectional and cohort studies were suitable for this meta-analysis. Reviews, intervention research, theses, and poster notifications were not included in the study. Studies with clinical populations (including infertility), studies with spouses of the clinical population, studies focusing on special populations of average or median age 65 and above, and studies conducted outside the field of health and social sciences were not included in the meta-analysis.

Data Extraction

The data to be collected from the studies were: authors and publication year of the study, the city and region in which the study was conducted, the average age of the sample, the method used for the diagnosis of MSD, ED or PE, total sample size, frequency or percentage of MSD, ED, and PE. After all the data were obtained, the collected information was rechecked by cross-exchange between the two researchers. If an error is detected, it is fixed.

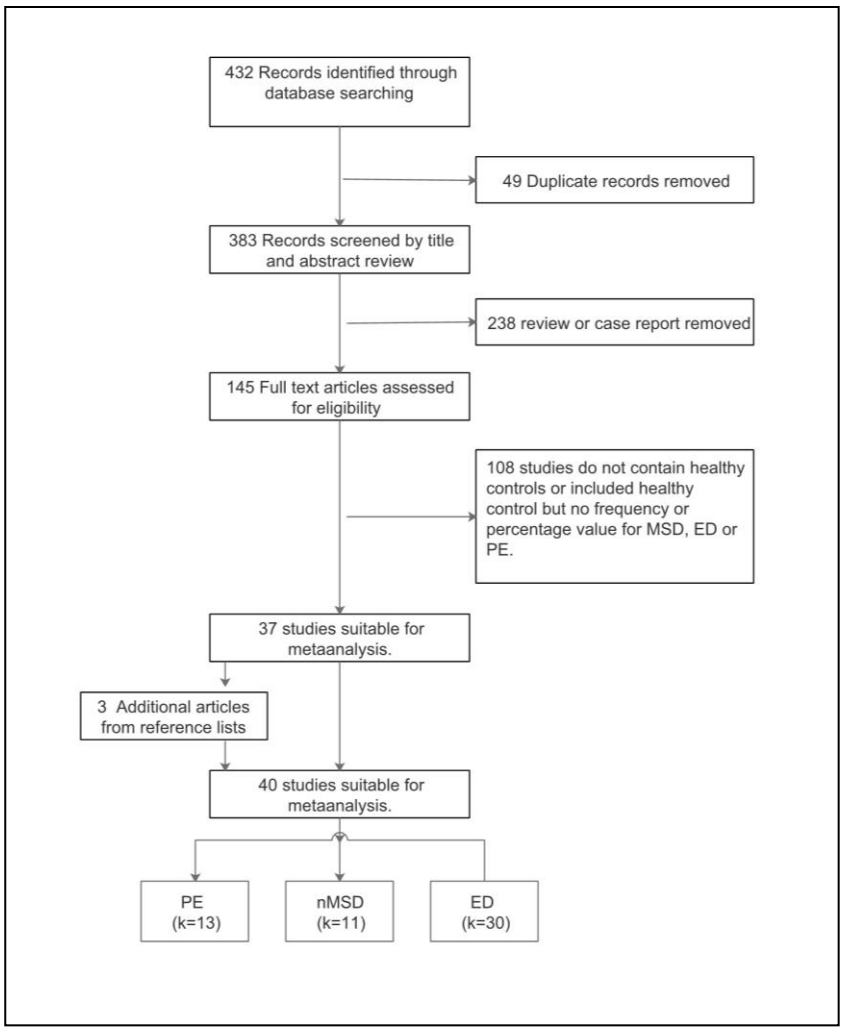

Figure 1. Flow diagram for study selection

Some of the data published publicly from the Turkish Statistical Institute's official website were used for meta-regression.[12] These variables were; Male first marriage age, crude marriage rate, crude divorce rate, literacy rate, and average gross national product per capita (GDP per capita -$-). These variables were added as moderator variables according to the publication year and region.

In the study, a meta-analysis of a single proportion method was used to calculate the effect size. For this, the number of cases with MSD, ED or PE and total sample sizes were recorded from each study. Weighted average ages were obtained for each MSD group using the average ages specified in each study. As explained below, the quality assessment was made for each study and the "quality" continuous variable was created.

Assessment methods of MSD

Since the studies covering the last 19 years are included, and there are changes in the diagnostic systems during this period, all methods previously used in the literature were included. Among them were the Arizona Sexual Experience Scale (ASEX), Golombok-Rust Inventory of Satisfaction (GRISS), International Index of Erectile Function (IEFF), Florida Sexual Health Questionnaire (FSHQ), Premature Ejaculation Diagnostic Tool (PEDT), Premature Ejaculation Profile (PEP) scales, Sexual Health Inventory for Men (SHIM) and face-to-face interviews that were used frequently and whose validity and reliability was determined. All of these scales have been used in international studies, and their Turkish validity and reliability have been tested.[13-16] Although face-to-face interviews have a more comprehensive assessment and high validity, and they are not frequently preferred in MSD studies. However, it is still one of the diagnostic methods frequently used in psychiatric practice.[17] Classifications for MSD in men coded as nonspecific MSD, ED, and PE.

Quality Assessment

The quality assessment of all included studies was carried out using the adapted 14-item quality criteria checklist recommended by Kmet et al.[18] There are questions in this checklist that evaluate studies in some ways (for example: “is the purpose clearly stated?” or “is the study design clear and appropriate?”). Each question was given "0 points" for the answer "no", "1 point" for the answer "partially" and "2 points" for the answer "yes". Questions that were not valid for the study were coded as “na (not applicable)”, and these questions were excluded from scoring and calculation. The quality score was obtained by dividing the total score by the highest possible score. The final score is between 0 and 1. The publication quality is considered high for studies close to 1. Each study was evaluated independently by two researchers. In case of disagreement, a consensus was reached with the senior researcher of this study. These final scores were evaluated by meta-regression.

Data Synthesis and Analysis

For the meta-analysis of prevalence statistics, prevalence data were transformed into logit event rate data and weighted by sample size. Results were then converted back to non-logit prevalence data for ease of comprehension. Egger’s test was used to evaluate publication bias between studies. It was also taken into account in the asymmetry on the funnel plots.[19,20]

I^2 statistics (i.e., the proportion of total variation explained by variation between studies) was used to determine heterogeneity between studies. It is assumed that if this value is 75% and above, there is heterogeneity.[21] Meta-analysis was performed according to both fixed and random-effects models. Considering the heterogeneity, the results were interpreted according to the random-effects model. Pooled prevalence rates were calculated with 95% CI. Meta-regression was applied to demonstrate the effects of possible variables on

the prevalence of MSD, ED and PE. For this, log-transformed prevalence rates of MSD, ED, and PE of studies and some demographic variables provided by TSI were analyzed by the mixed-effects meta-regression method. Relationships between the prevalence of MSD, ED, and PE and predictive variables were visualized with graphs. R program used for analysis.[22,23]

Results

Study Characteristics

As a result of the screening, 432 studies were reached. Forty-nine of these studies were duplicated studies. According to the article titles, 238 reviews and case studies were excluded. The abstracts were examined and 108 studies were excluded because they did not contain healthy controls and they did not report frequency or percentage rates, although they included healthy volunteers. As a result, 40 studies were included in the meta-analysis as they provided appropriate data. Meta-analysis was performed separately for MSD, ED, and PE. The number of studies for each meta-analysis was as follows: 11 studies for MSD, 30 studies for ED, and 13 studies for PE. The flow chart of the scanning method is shown in figure 1. The studies included meta-analysis conducted in 17 different provinces of Turkey. Eight studies are multi-center studies conducted in more than two provinces. The cities where most studies are conducted are Ankara and Istanbul, respectively. ASEX for MSD, face-to-face interviews for PE, and IIEF for ED was the most common assessment methods.

Prevalence of MSD, ED and PE in the general population

In the studies analyzed for the prevalence of ED, the total number of healthy volunteer men was 8874 (min=20, max=2288) and the weighted average age was 37.32 (min=20.44, max=61.11). Considering the random-effects model (Heterogeneity analysis results: Q value = 1606.42, df (Q)=29, p <0.001, I^2 = 98.22% (97.87%-98.48%), Tau square = 1.499) prevalence of MSD was found to be 17.83% (11.89%-25.72%). According to the fixed effects model, it was found as 31.77% (30.63%-33%) (Figure 2). Thirty studies were included in the analysis and the average study quality score was 0.68±0.14. Egger's test results for publication bias: t = - 1.338 and p = 0.010. According to these results, it can be said that there is publication bias (Figure 5).

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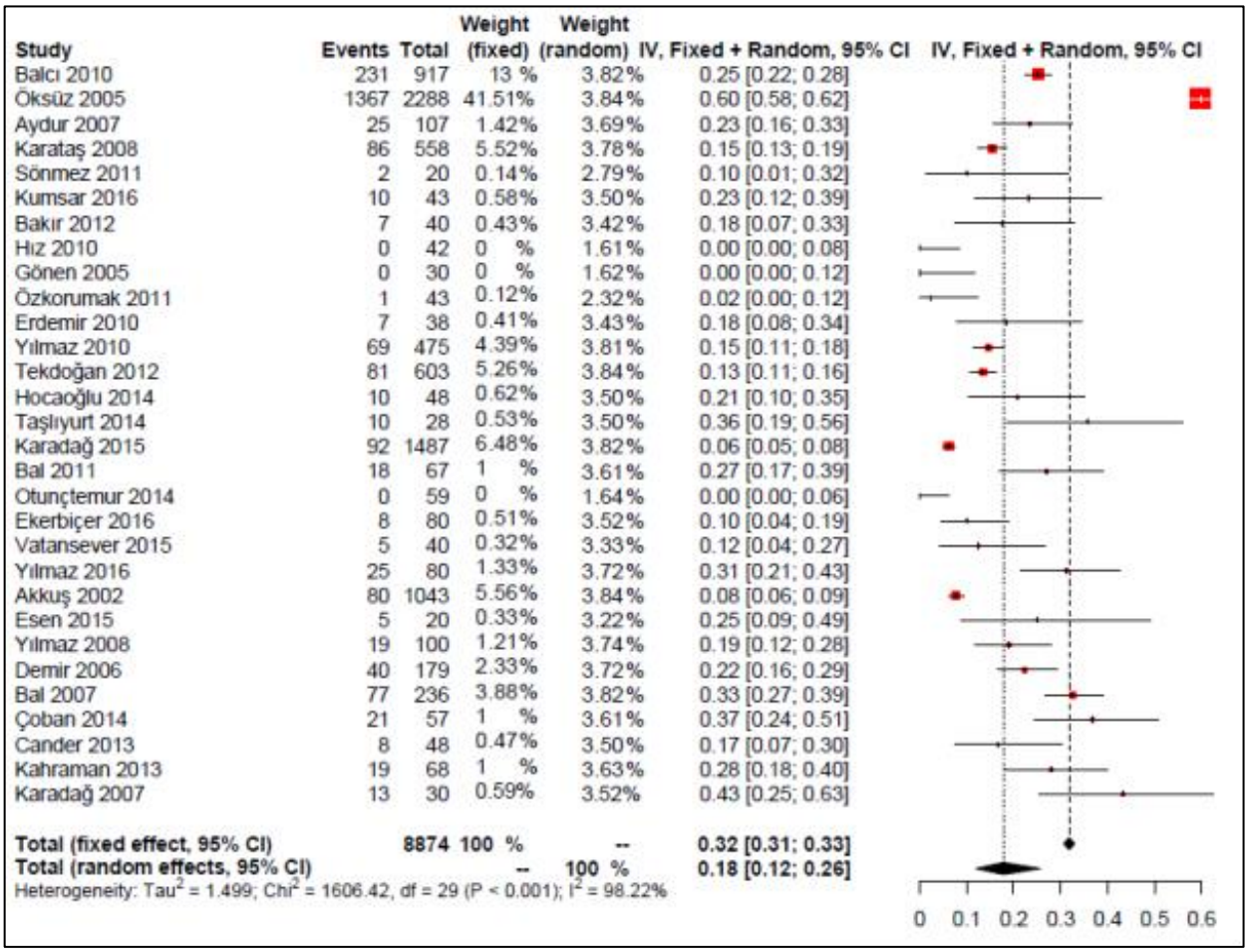

Figure 2. Forest plot for erectile dysfunction

In the studies analyzed for the prevalence of MSD, the total number of healthy volunteer men was 5999 (min=20, max=2760), and the weighted average age was 41.56 (min=28.24, max=54.19). Considering the random-effects model (Heterogeneity analysis results: Q value=126.29, df(Q)=10, p <0.001, I^2 = 92.14% (87.82%-94.86%), Tau square = 0.136) prevalence of MSD was found to be %27.50 (%22-%33.81). According to the fixed effects model, it was found as %37.82 (%36.58-%39.14) (Figure 3). Eleven studies were included in the analysis and the average study quality score was 0.67±0.14. Egger's test results for publication bias: t = - 1.860 and p=0.095. According to these results, it can be said that there is no publication bias (Figure 5).

In the studies analyzed for the prevalence of PE, the total number of healthy volunteer men was 10235 (min=20, max=2593) and the weighted average age was 33.73 (min=20.42, max=41.87). Considering the random-effects model (Heterogeneity analysis results: Q value=1160.84, df (Q)=12, p <0.001, I^2 = 99% (98.72%-99.21%), Tau square =0.821) prevalence of PE was found to be %24.22 (%16-%24.68). According to the fixed effects model, it was found to be 29.91% (28.93%-30.86%) (Figure 4). Thirteen studies were included in the analysis and the

average study quality score was 0.70±0.15. Egger's test results for publication bias: t = - 0.935 and p=0.369. According to these results, it can be said that there is no publication bias (Figure 5).

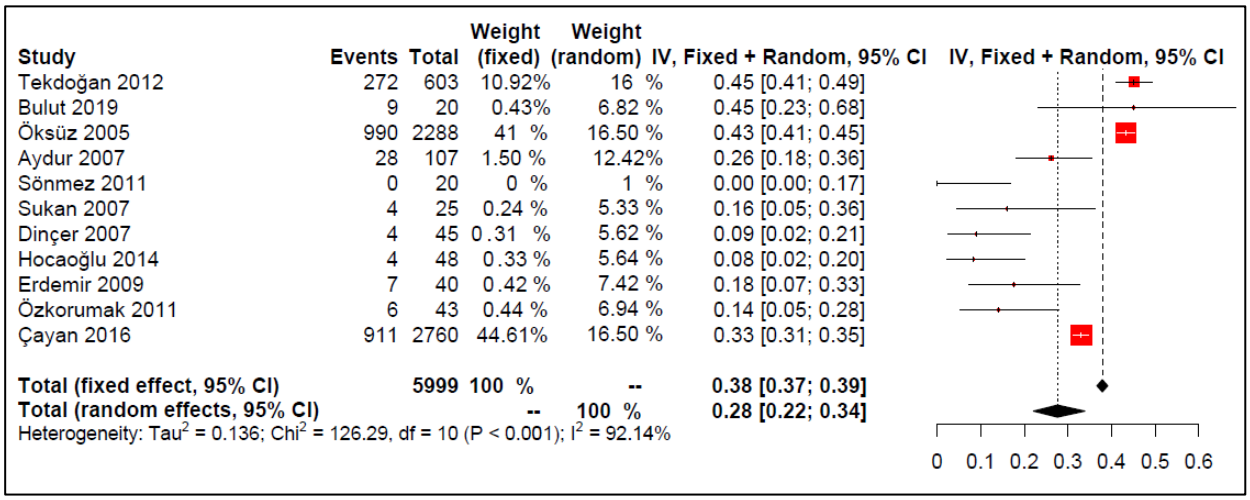

Figure 3. Forest plot for nonspecific male sexual dysfunction

Meta-regression Results

If there is high heterogeneity between studies, meta-regression is applied to reveal the factors that may cause this heterogeneity. Since significant correlations vary between medium and very high among many of the predictor variables previously described, the effects of these variables on the prevalence of MSD, ED, and PE were investigated by separate meta-regression models.

In studies on ED (k = 30), only the evaluation method had a significant effect on ED prevalence (When the reference category is accepted as the face-to-face interview; β_{FSHQ}=2.526, p <0.001, and β_{IIEF}=0.869, p=0.024, R^2=68.83%. For other assessment tools; p >0.05). None of the other variables, including age, had a significant effect.

In studies on PE, we found that the crude divorce rate and the publication year of the study had a significant effect on PE prevalence ($\beta_{Crude\ Divorce\ Rate}$=1.584, p=0.053, R^2=7%, k=11 and β_{Time}= - 0.125, p=0.002, R^2=67.33%, k=13). No significant effect of other variables was detected.

Considering studies evaluating male sexual dysfunction as non-specific, the effects of female first marriage age, male first marriage age, male-female first marriage age difference and crude divorce rates on MSD prevalence have a significant effect ($\beta_{First\ marriage\ age\ women}$= -0.382, p=0.026, R^2=6.9%, k=10; $\beta_{First\ marriage\ age\ man}$= - 0.379, p=0.018, R^2=12.88%, k=11; $\beta_{Difference\ Between\ Age}$= -1.856, p=0.012, R^2=15.84%, k=10; $\beta_{Crude\ Divorce\ Rate}$= 1.341,

p<0.001, R^2=34.93%, k=10). Other variables have no significant effect. The regression graphics of all models are shown in Figure 6.

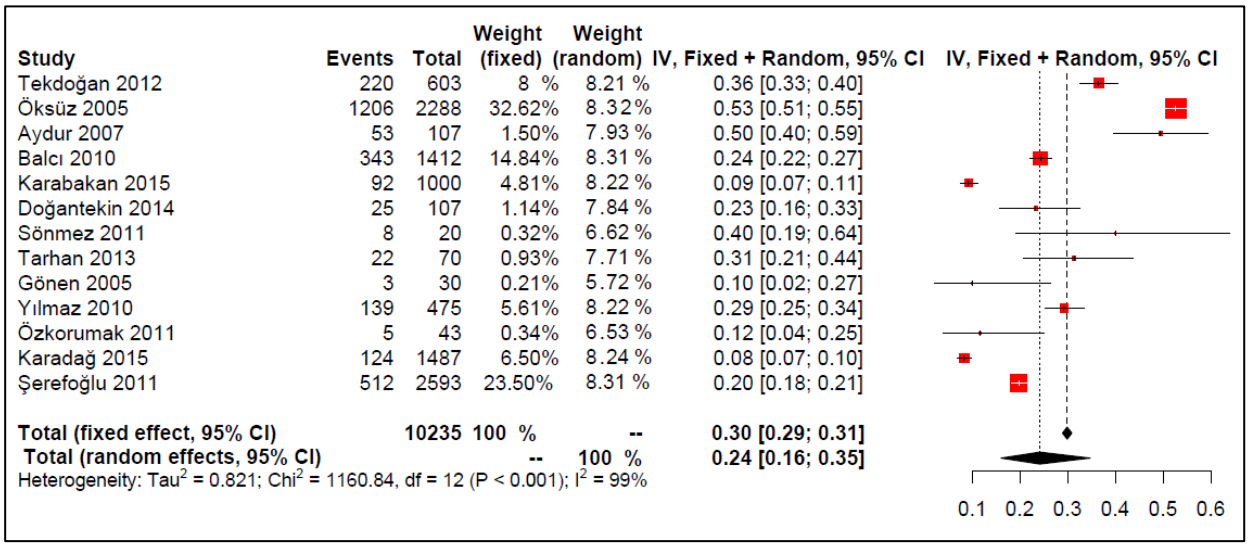

Figure 4. Forest plot for premature ejaculation

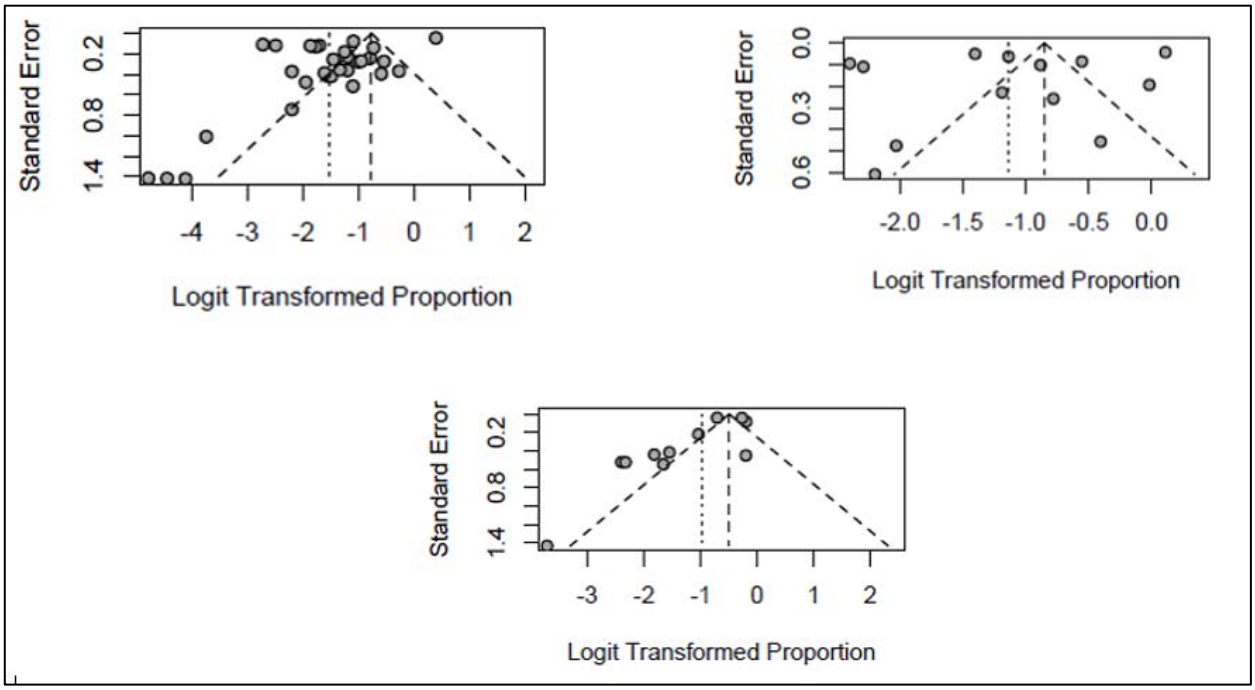

Figure 5. Funnel plots for erectile dysfunction, premature ejaculation and nonspecific male sexual dysfunction

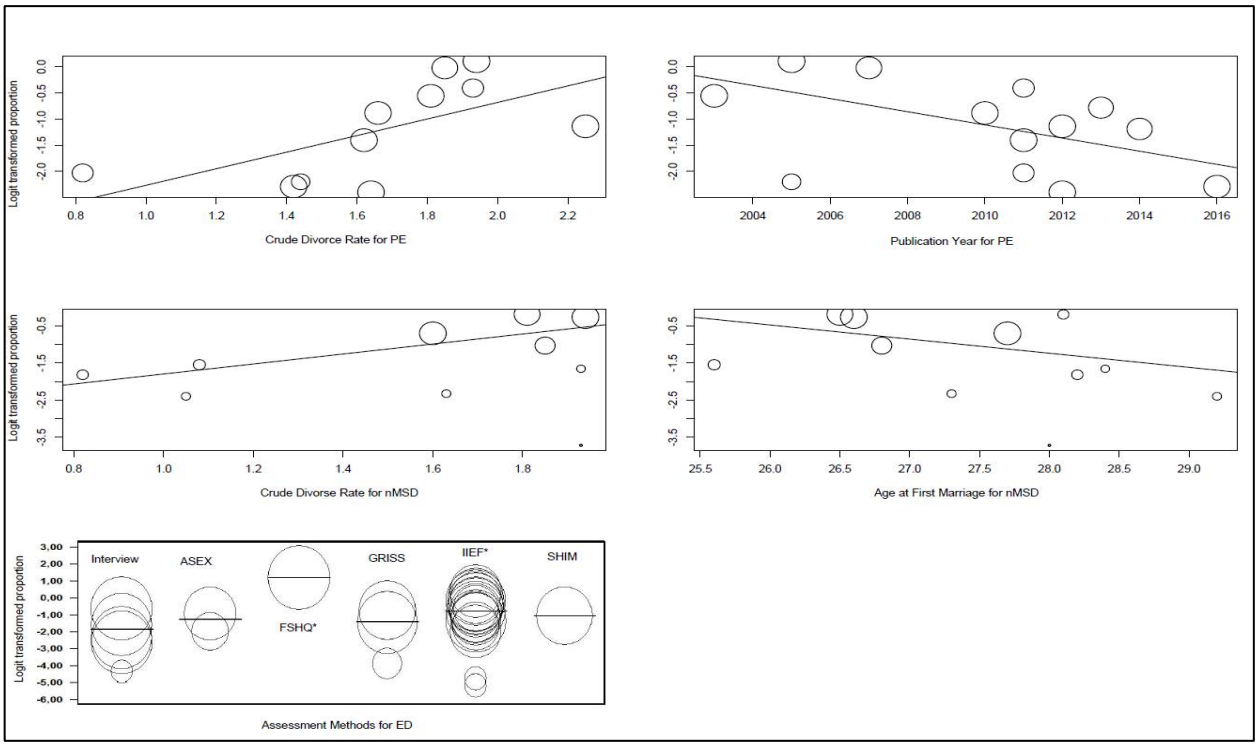

Figure 6. Meta-regression models for erectile dysfunction, premature ejaculation and nonspecific male sexual dysfunction

Discussion

The MSD is mostly seen as ED and PE. However, SD can be considered dimensionally as well as categorically. Multiple sub-threshold symptoms may not be diagnosed with ED or PE. However, a more general, inclusive, nonspecific or overall SD classification based on the total scores of the scales is also used, especially in the research area rather than in clinical practice. In our study, the equivalent of this is MSD. We found the prevalence of MSD 28%. In the literature, male sexual health is mainly categorically handled. In one study, overall MSD was reported as 66%[24] and in another study as %31.[17] Our study appears to be the first prevalence of MSD reported based on a meta-analysis.

In our study, we found the prevalence of erectile dysfunction as 18%. Studies reporting the prevalence of ED have reached very different results, such as 5-79%.[8,9,25] These different results appear to be due to two main reasons. First, the sample may not represent the general population (i.e., a small sample, an elderly sample, a sample of individuals with medical disease, or a sample in cultural subgroups). The second is the differences in ED evaluation methods. As a matter of fact, in our study, IIEF is the most commonly used method in ED evaluation, but six different methods were used. Also, the lack of a single cut-off point for ED in evaluation

methods is another problem. In some studies, accepting even "mild" cases as ED may have caused different and high prevalence rates. In our study, we accepted the "mild-moderate" level and above as ED.

In our study, the prevalence of PE was 24%. Studies on PE prevalence seem to yield relatively more consistent results than ED studies. Indeed, the prevalence of PE has been reported to be 20-31 %.[9,25]

As far as we can see, there is no meta-analysis study on SD prevalence in men to represent the men aged 18-65. Our work is first in this sense. However, our meta-analysis is a national study and a meta-analysis covering international studies is needed.

Meta-regression

There is high heterogeneity among studies, including meta-analysis. Our study has shown that the reason for this heterogeneity is not the quality of the included studies. MSD is under the influence of many biopsychosocial factors. Meta-regression results may shed some light on these possible factors.

According to our results, FSHQ and IIEF diagnose significantly higher ED than other assessment methods. IIEF identifies mild, mild-moderate, moderate, and severe cases for the diagnosis of ED. Therefore, it can be defined as a compassionate measuring tool. For this reason, some “sub-threshold” cases may be categorized as ED even if there is no disorder. When the FSHQ Turkish validity study is examined, it is understood that the items measuring erectile dysfunction are K, L, M, and P items. However, item M is a question about infertility. In addition, it was observed that the J question (premature ejaculation) was loaded with similar weight in the ejaculation dimension along with the erection dimension. In other words, the Turkish version of this scale may evaluate infertility and premature ejaculation while evaluating male dysfunction. Therefore, ED scores may be high.

As the age increases, the frequency of ED or MSD is expected to increase.[26] However, in our study, we did not find a significant relationship between ED or MSD prevalence and age. A possible reason for this result may be the average age of the sample collected for meta-analysis to be 37.32 for ED and 41.56 for MSD. The average age in a single study is 61. Apart from this study, the average age in all studies is below 60, and the number of studies under the age of 45 is relatively much higher. It has been reported that testosterone levels decrease by 1.50% each year after the age of 40 in men, but this decrease is faster after the age of 60. Also, the decrease in testosterone in men and associated sexual dysfunction is not as fast as in women and shows differences between individuals. [27] It can be said that our samples are not old enough to cause MSD or ED, and this sample is homogeneous in terms of sexual psychophysiology. A second explanation is that the meta-analysis sample consists of men aged 18-65, considered healthy people. Probably it is not only age-related changes that increase the risk of ED or MSD, but also what increases the risk are systemic diseases such as diabetes and hypertension,

which increase in frequency with age. Our meta-analysis was conducted with a sample selected from men aged 18-65, considered healthy. Therefore, the number of individuals with comorbid diseases is relatively low. This may explain our results regarding the relationship between age and ED or MSD.

According to the results of our study, the prevalence of PE decreases over time. Unlike ED, PE is more affected by psychosocial factors. Risks for PE may be reduced by increasing knowledge and experience about sexual health over the years. Of course, effective treatment may have caused these results. An interesting and controversial result regarding PE and MSD is the high frequency of PE in populations with high divorce rates. Healthy sex life is one of the essential components of couples' maintaining a healthy relationship. Therefore, male or female sexual dysfunctions may contribute to divorces by negatively affecting this relationship. Of course, the relationship between divorce and PE and MSD can also be addressed from the other side. In other words, problems in the relationship quality of the couple may negatively affect the sexual health of the couple.

Finally, meta-regression models point to a negative relationship between the prevalence of MSD and the male age at first marriage. The positive effects of long-term and regular sexual life and consequently increased sexual knowledge and experience on sexual health may explain this result.

Advantages and limitations of the study

This study is the first meta-analysis study on the prevalence of MSD, ED and PE in Turkey. It presents epidemiological data on MSD, ED and PE in detail. It also provides information on possible factors affecting the frequency of MSD. The results of this study show that male sexual dysfunctions are common in the general population. Male sexual dysfunctions, especially PE and some ED patients, are treatable diseases, they generally respond well to psychosocial interventions, and as a public health problem, preventive and therapeutic approaches are definitely needed.[28] In this way, the quality of life and well-being will increase both directly (healthy life) and indirectly (the contribution of healthy sex life to physiology and psychological health).

One of the limitations of the study is the high I^2 values, that is, heterogeneity between the studies. In prevalence studies, very different results can be reported due to reasons such as study design, classification of the related disorder, assessment tools, the publication year of study, and regional differences.[29] Although meta-analysis studies provide more reliable results on prevalence rates, heterogeneity between studies is still a disadvantage. However, heterogeneity is not uncommon in many meta-analysis studies.[30] This limitation was tried to be overcome by using “random” models in the analysis. Another limitation concerns some variables included in meta-regression. First, these variables were collected from the official website of TSI and reflect the demographic and cultural characteristics of the region where the study is conducted. However, it should be noted that most of the studies included in the meta-analysis do not include such variables. Finally, it should be

underlined that differences in the measurement and determination of sexual dysfunctions, study designs, and publication quality should be taken into account in the interpretation of results.

The prevalence of MSD, ED, and PE in Turkey is similar to the results of other international prevalence studies. However, treatment facilities and access to these facilities are relatively limited and need to be developed to meet the needs.

Ethical considerations: Since this is a meta-analysis study, application to an ethics committee was not required. Only publicly available data were used in the study.

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Conflict of Interest: The authors declare that there is no conflict of interest.

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Research Article

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GLYCEMIC REGULATION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS: EFFECTS OF MOTIVATIONAL INTERVIEWING

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Abstract

Objectives: Motivational interviewing (MI) is a convenient and effective counseling technique with positive effects on patients with Type 2 Diabetes Mellitus (T2DM), which provides a positive influence on their treatments/follow-up and help them to adopt health-enhancing behaviors. This study investigates whether MI has an effect on improving glycemic control in T2DM patients.

Materials and Methods: This is a retrospective study enrolling 76 follow-up T2DM patients at a family health center who received MI. As a control group, age- and gender-matched 33 T2DM patients who were followed at the same family health center and did not receive MI were recruited. All patients were compared for their age, gender, marital status, education status, duration of diabetes, and HbA1c levels.

Results: In the MI group, T2DM patients had a mean follow-up duration of 22.63±11.93 (3-38) months vs. 24.33±11.29 (3-36) months in the non-MI group (p=0.489). At the end of this follow-up period, the HbA1c level dropped from 8.30±2.10% to 7.68±1.48% (p=0.006) in the MI group, whereas the decrease in the non-MI group was from 8.12±2.14% to 7.93±1.16% which was not statistically significant (p=0.504).

Conclusion: In this study, it was shown that MI provided a significant decrease in HbA1c levels in T2DM patients. MI helps blood sugar regulation by creating lifestyle changes in T2DM patients. MI is a method that can be applied in clinical practice by family physicians working in primary care, who play an important role in the follow-up and treatment of T2DM patients.

Keywords: Motivational interviewing, diabetes mellitus, family physician, blood glucose regulation.

Introduction

In Turkey, as in the entire world, the incidence of type-2 diabetes mellitus (T2DM) is ever-growing, making it a major public health problem. According to The Turkish Epidemiology Survey of Diabetes, Hypertension, Obesity and Endocrine Disease (TURDEP) 1 and 2 studies which were conducted in 1998 and 2010, respectively, within the elapsed time period rate of increase in Diabetes Mellitus (DM) was 90% and in obesity was 44% (The incidence of DM was 7.2% and 13.7% in TURDEP 1 and 2, respectively).[1] The data from the International Diabetes Federation (IDF) Diabetes Atlas 9th Edition suggests that by 2025, Turkey will be among the top 10 countries with the highest number of DM patients having an estimated 10.4 million DM patients.[2] Fighting with T2DM shall incorporate an integrative approach entailing decelerating the rate of disease development along with promoting the "health behavior change" in DM patients during their follow-up and treatment. At the early and advanced stages of T2DM, health-enhancing behaviors include adopting an adequate and balanced diet, regular exercise, self-monitoring of blood glucose, and timely and accurate dosing of medication. When effectively applied, such behavior changes help increase the quality of life and decrease macro- and micro-vascular complications in patients.[3]

Studies on health behavior change have documented a number of models, of which the Transtheoretical Model (TTM) is the most common one, readily applicable to many aspects of health behavior.[4,5] For patients with T2DM, motivational interviewing (MI) has been shown as a convenient and effective TTM-based counseling technique with a beneficial impact on follow-up and treatment of DM patients.[6] Such positive impact arises from the favorable effect of MI on lifestyle change as well as on psychological conditions, including emotional stress and depression, which are of utmost importance in DM.[7]

TTM is composed of 6 stages called pre-contemplation, contemplation, preparation, action, maintenance and termination. The ultimate aim at the end of these stages is to have the patient adopt health behavior changes that include gaining habits such as proper use of medication, adequate and balanced diet, and regular exercise. This study was conducted at a primary family care center where TTM was used to administer MI to T2DM patients aiming to investigate whether it is effective in blood sugar regulation.

Materials and Methods

This study was carried out at a family health center in patients who were diagnosed with T2DM and followed up between July 2015 and October 2018. This study was ethically and scientifically approved by the local Non-Interventional Clinical Research Ethics Committee with decision number 14 on 17th March 2020. In addition, necessary permissions were obtained from the Provincial Health Directorate for the study.

Patients and Control group

This is a retrospective case-control study of T2DM patients with and without MI. Patient age, gender, medication history, education status, marital status, duration of DM, ongoing medication, and glycated hemoglobin (HbA1c) levels were retrieved through the hospital automation system, and patient records were available to the family health center. In the MI group (76 patients), follow-up duration was calculated as the time elapsed from the date of the first interview to the date of study data cut-off. The inclusion and exclusion criteria of the study were as follows.

Inclusion criteria: (a) Being aged over 18 (b) Patients with a diagnosis of T2DM (c) Having a motivational interview for at least three months (d) Presence of HbA1c values at the time of enrollment and at the end of the study.

Exclusion criteria: (a) Patients with a diagnosis of type 1 DM (b) Patients younger than 18 years old (c) Absence of HbA1c value (d) Patients who did not comply with follow-up.

The control group was composed of age- and gender-matched 33 T2DM patients who did not undergo MI but were followed and treated at the same family health center.

The follow-up period of the patients included in the study was calculated as the time between the start of the MI and the date the study data were collected. In terms of HbA1c values, the initial HbA1c value was taken as the value at the beginning of the MI interview, and the final HbA1c value was taken as the value at the end of the study.

Motivational interview method

Patient interviews were implemented with a technique developed by Miller and Rollnick at the usual outpatient clinic setting as sessions over an average of 15 minutes. MI was conducted in 4 phases, namely, engagement, focusing, evocation, and planning, which may occasionally be intertwined or follow a different sequence of occurrence. [8]

During the *engagement* stage, a common language and a collaborative environment were built. Face-to-face interviews were held in an environment without a barrier in between, e.g., a table. A rapport relying on mutual reliance and respect was sought.[8]

Focusing involved open-ended questions such as "What do you know about diabetes? "What is bothering you at most, lately?" and patients were given information based on their replies. The information given was predominantly about the topic the patient was willing to talk about. Thus, patient autonomy was respected.[8]

In the *evocation* stage, the interviewer has taken an attitude in line with the type of talk (change and sustain talk) arising during the interview. The more the patient makes change talk, the closer she or he is to the change. Therefore, the patients were encouraged toward change talk and questions were directed to elicit change talk. During the conversation, various methods were followed, such as looking at the past (I see here you had a low HbA1c 2 years ago, how did you manage that?), looking at the future (Can you please list three reasons why to take your blood sugar under control?) eliciting a reason for the change (What do you think will happen in the future, if things keep going like this?), questioning extreme cases (What can happen in the future at worst?), drawing out goals and values (What is important to you in this life?) and exploring ambivalence.[8]

At the stage of *planning,* the patient is more engaged in change talk, with a lesser amount of sustain-talk. We have discussed what obstacles may hinder the patient from achieving the change and how to overcome them.[8]

All these stages were implemented at varying weights and durations considering the progress attained by the patient and were all recorded. In this study, the data extracted from such records were used.

Statistical analysis

Statistical analyses were carried out using the program SPSS version 20.0. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were expressed as frequency and percentage. Shapiro Wilk's test was applied to check whether the data has a normal distribution. Depending on whether they have a normal distribution or not, continuous variables were analyzed using the Mann-Whitney U test or independent samples t-test, and categorical variables were analyzed using Pearson's chi-square test. Statistical analysis results within a confidence interval of 95%, and the p-value of <0.05 was accepted as statistically significant.

Results

At the end of the study, 76 patients in the MI group (51 female, 25 male) were not different from the 33 patients in the non-MI group (21 female, 12 male) in terms of their age, gender, marital status, education status, medication, or duration of follow-up. Clinical and laboratory features of patients are shown in Table 1.

Table 2 shows the change in HbA1c levels of the patients. There was no difference in the baseline HbA1c level, which was measured at the time of study entry, between the MI group and non-MI group (p=0.697). At the end

of the follow-up duration, however, the mean HbA1c level in the MI group decreased by 0.62±1.89% (a decrease of 7.04% from the initial value), whereas the decrease in non-MI was 0.19±1.65% (decrease of 1.58% from the initial value) (Graphic 1). There was a statistically significant decline in the MI group (p=0.006).

Table 1. Clinical and laboratory characteristics of patients

	Receiving MI (n=76)	**Not receiving MI (n =33)**	**p**
Age (mean±SD)	56.07±9.29	58.79±11.49	0.194
Gender Female, n, (%) Male, n, (%)	 51 (67.11) 25 (32.89)	 21 (63.64) 12 (36.36)	0.826
Marital Status Married, n, (%) Single, n, (%)	 54 (71.05) 22 (28.95)	 27(81.82) 6(18.18)	0.340
Educational Status Literate, n, (%) Primary School, n, (%) Secondary School, n, (%) High School, n, (%) University, n, (%)	 21 (27.63) 30 (39.47) 9 (11.84) 11 (14.47) 5 (6.58)	 4(12.12) 16(48.48) 5(15.15) 6(18.18) 2(6.06)	0.515
Medication OAD, n, (%) OAD + Insulin, n, (%)	 61 (80.26) 15 (19.74)	 27 (81.81) 6 (18.18)	0.850
Time of follow-up (Month)	22.63±11.93 (3-38)	24.33±11.29 (3-36)	0.489

(MI: Motivational interviewing, OAD: Oral antidiabetic)

Table 2. The Hb1Ac levels of patients

HbA1c (%)	**Receiving MI (n=76)**	**Not Receiving MI (n =33)**	**p**
Start (mean ±SD)	8.30±2.10	8.12±2.14	0.697
End (mean ±SD)	7.68±1.48	7.93±1.16	0.405
Start–End difference (mean ±SD)	0.62±1.89*	0.19±1.65**	

*p=0.006, **p:0.504

(Hba1c: Glycated hemoglobin, MI: Motivational interviewing)

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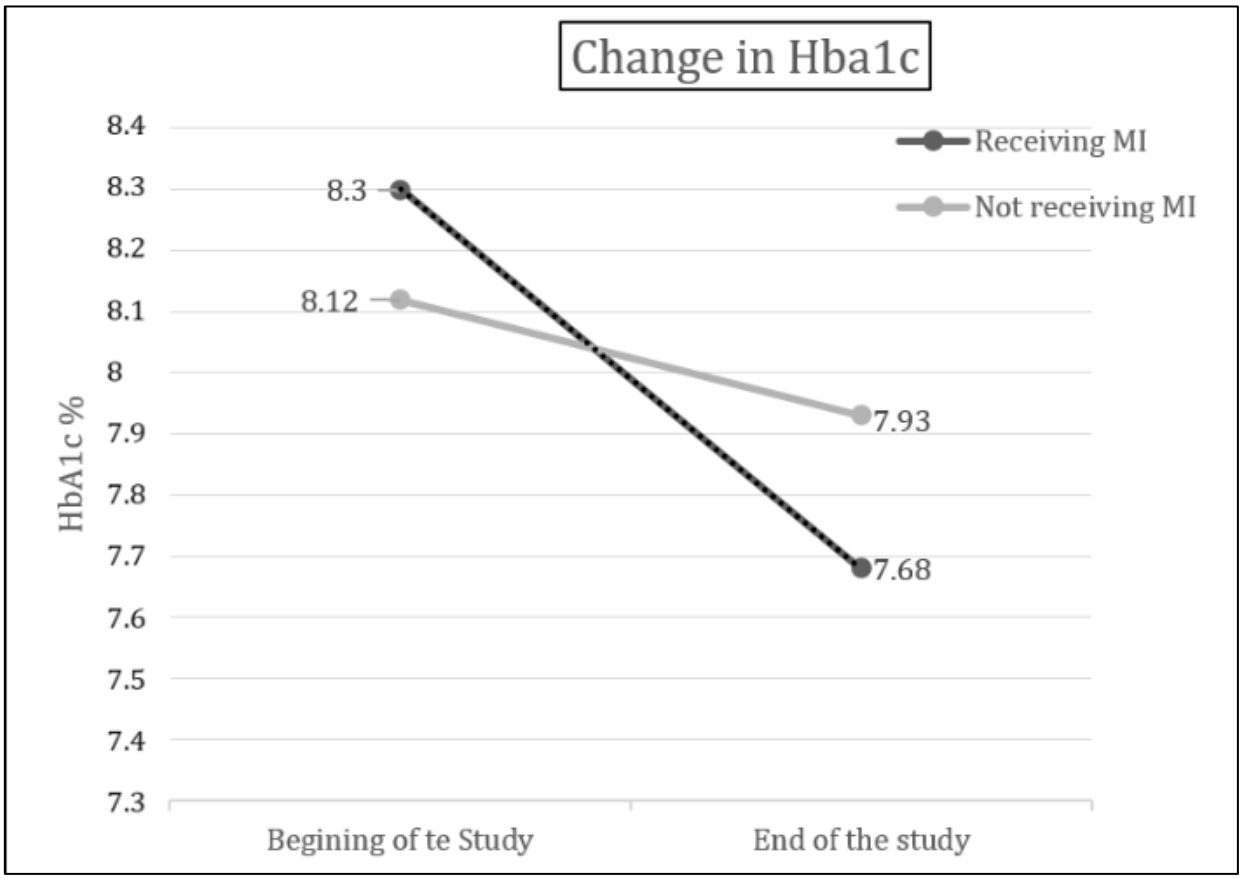

Figure 1. HbA1c change at the end of the study

Discussion

In this study, our aim is to investigate whether MI has an effect on blood sugar regulation, and we found a greater decrease in HbA1c levels of the patient who were subject to receiving MI compared to those who did not receive MI. While the average decrease in HbA1c was 0.62% in the group that received MI, it was only 0.19% in the group that did not receive MI.

All national and international guidelines recommend first-line lifestyle changes for T2DM patients. As such, the T2DM treatment guideline of the American Diabetes Association (ADA) highlights lifestyle changes play an important role both in the prevention of DM development and in the course of the disease and recommends medication shall be initiated when necessary.[9] Moreover, former research has demonstrated that lifestyle change is not only effective in achieving an HbA1c decrease in diabetic patients but also may help reduce the rate of T2DM development in pre-diabetic individuals by 40-58%.[10-12] Although lifestyle change is an efficient

method both in the prevention and treatment of diabetes, professionals in diabetes training claim behavior change is indeed the most challenging part of enhancing the health of diabetic individuals. From a behavior change perspective, it is further stated that traditional, advise-imposing attitudes that are frightening for the patient are putting barriers. Instead, counseling techniques that involve reinforcement and training for the patient, attempting to understand the patient in psychosocial aspects and changing behavior in the short term are facilitators.[13] There is no shortage of studies that report that MI, one of the techniques capable of behavior change, as well increases lifestyle change.[14-16] Provided that they are administered with a correct approach, MI strategies are adaptable to encourage self-care practice in diabetes, including a healthy diet/meal planning, physical activity, psychosocial adjustment, foot care, home blood sugar monitoring, medication adherence, and medical follow-ups oriented to assure lifestyle change in diabetes.

In the majority of studies in patients diagnosed with T2DM, MI features out with a potential to facilitate lifestyle change in comparison to other interventions based on its effectiveness and interactive nature. While results from most of the studies indicate MI has contributed to positive change in self-care activities such as healthy diet/meal planning, physical activity, foot care, and home blood sugar monitoring, some studies did not find a significant difference in diabetes-related self-care behaviors following MI.[16-20]

On the other hand, studies exploring the effects of MI on regulating blood sugar and decreasing HBA1c have controversial results. While several studies have detected a significant improvement in HbA1c levels in patients who have undergone MI, another study identified that patients had improved regardless they received MI or not. [21-24] Similarly, in the study conducted by Ismail K. *et al.* in 2018, MI had no effect on HbA1c levels.[25] A systematic review and meta-analysis carried out in 2014, the results from 13 studies of 1223 type-1 DM and 1895 T2DM patients were analyzed.[26] According to this analysis, the authors state the improvement in glycemic control in the MI patient group was 0.17% which was not statistically significant. In our study, on the other hand, the decrease in HbA1c levels, which stands for the improvement in glycemic control, was greater in the MI group compared to the group without MI. The decrease achieved in the HbA1c level was statistically significant in the MI group ($p=0.006$), whereas no significant decrease was noted in the group who were not interviewed ($p=0.504$).

In this study, although we have demonstrated improvement in glycemic control through MI, upon which we also have detected recoveries in certain lifestyle changes, there were some limitations. First, of these, we did not use any scales to score lifestyle changes in this study. But still, we have observed and noted through our conservations with the patients we had administered MI that these patients were more informed about their disease, they were taking their medication more properly and timely, and they had better self-care. We have identified patients who got used to lifestyle changes such as adherence to the prescribed diet, getting regular exercise, and avoiding food that may elevate their blood sugar levels. Of note, advising the patients regarding

the meaning of HbA1c level as a criterion for the DM follow-up and assigning them responsibility concerning what must be done to decrease it helped foster patient motivation. Secondly, the number of patients included in the study was small. Third, patient follow-up times are partially heterogeneous. Finally, the study design is retrospective. The effects of motivational interviewing on blood sugar regulation can be demonstrated with a larger number of patients and in longer-term prospective studies.

Consequently, in this study, it was shown that motivational interviewing provided lifestyle changes (cessation of smoking, exercise, and alcohol cessation) in individuals with diabetes, resulting in improvement in glycemic control. In all national and international diabetes treatment guidelines, providing lifestyle change is one of the first-line treatments, and special attention is paid to this. Family physicians, one of the health professionals who play an important role in the treatment of diabetes, can also use this method to provide lifestyle changes by applying motivational interview techniques.

Ethical Considerations: Our study has been planned according to the Decisions of the Helsinki Declarations, and the required permission for the research has been granted by the local Clinic Research Ethical Board on 17th March 2020, with decision number 14.

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

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Research Article

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A CROSS-SECTIONAL STUDY EVALUATING COVID-19 VACCINE LITERACY: THE EXAMPLE OF ANTALYA PROVINCE

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Abstract

Objectives: It is believed that the COVID-19 pandemic, which is a significant health concern, can be restrained through effective vaccination. In this regard, however, people's hesitancy toward vaccines stands out as an important obstacle to achieving community immunization. The aim of this study is to evaluate the factors that affect individuals' decisions to get a COVID-19 vaccine and to identify their literacy status for COVID-19 vaccines.

Materials and Methods: This study consisted of 388 people aged 18 and over who presented to the COVID-19 adult vaccination outpatient clinic at the University of Health Sciences Antalya Training and Research Hospital between July 1st and September 1st, 2021. The participants were asked a number of questions contained in the COVID-19 vaccine literacy scale, and answers were recorded.

Results: The participants' mean vaccination literacy score was considered moderate within the range of 2.95 ± 0.54. The results revealed that the higher the education level of the participants, the higher the COVID-19 vaccine literacy, and that the COVID-19 vaccine literacy was higher among individuals who voluntarily got vaccinated.

Conclusion: By recognizing that individuals may have hesitancy about vaccination, relevant strategies should be developed for the vaccination with the aim of giving information to and instilling confidence in society rather than causing fear.

Keywords: COVID-19, health literacy, vaccine hesitancy, vaccine literacy.

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Introduction

The management of the COVID-19 pandemic, which is an important health concern not only in our country but all over the world, is intended to protect health and prevent the spread of the COVID-19 virus by means of measures aimed at people and the environment. In addition to the measures, the devastating consequences of the disease have been sought to be prevented through scientific vaccine studies and vaccination that have gained momentum recently. In this respect, mRNA vaccines, viral vector-based vaccines, inactivated vaccines, and protein subunit vaccines developed for this purpose are the main approved vaccine types tested in clinical trials against the COVID-19 virus.[1]

Vaccination is an essential health service that aims at community immunization against diseases, and it is the right of every individual to receive health care. However, it is absolutely necessary that people know their rights and responsibilities, as much as the importance of healthcare services they are offered in terms of personal and social aspects, so that an effective level of healthcare service can be achieved. Individuals are active decision-makers in the process of receiving the healthcare service, and their level of benefit from such services is directly related to the extent of their health literacy level.[2]

With the availability of COVID-19 vaccines, it is no longer a major barrier for most countries, yet people's hesitancy to get vaccinated remains a major challenge.[3] In addition to problems such as not believing in the severity of the disease or the efficacy of the vaccine, as well as the concerns about possible side effects, misinformation also significantly affect vaccine acceptance.[4]

Within the same scope, vaccine rejection is an individual attitude that affects the entire society, and the idea of vaccine rejection spreads through interpersonal communication, especially through social media, leading to negative consequences in terms of community immunization.[5] Instead of getting an expert opinion on health, some people tend to seek treatment by receiving advice from other people whom they communicate with on the Internet and social media.[5] The main reason for vaccine hesitancy is considered as the sense of insecurity towards healthcare systems, and health literacy is believed to be a mediating factor in overcoming insecurity and vaccine hesitancy.[6] By collecting relevant data on the following aspects, such as the factors influencing people's decisions to get a COVID-19 vaccine, whether they can get access to sufficient information about vaccination, as well as the extent that they discuss the information they have gained with other individuals, this study has aimed to evaluate the literacy levels of individuals for the COVID-19 vaccine.

Materials and Methods

Study design and participants

This cross-sectional and observational study consisted of people aged 18 and over who presented to the COVID-19 adult vaccination outpatient clinic at the University of Health Sciences Antalya Training and Research Hospital between July 1st and September 1st, 2021, and volunteered to be involved in a clinical trial.

After the participants were asked questions about their sociodemographic characteristics, how they decided to get vaccinated, and their thoughts on COVID-19 vaccines in a face-to-face interview, they were asked the questions in the COVID-19 Vaccine Literacy Scale, and the answers were recorded.

Prior to the study, approval was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Antalya Training and Research Hospital as of 24.06.2021 with decision number 9/6. The study was conducted in accordance with the Declaration of Helsinki.

COVID-19 Vaccine Literacy Scale

Durmuş et al. conducted the construct validity and reliability of the Turkish version of the scale, which was originally developed by Ishikawa et al. and adapted as a COVID-19 vaccine literacy scale by Biasio et al.[7-9]

The scale consists of 12 questions, the first 4 of which aim to assess functional skills and the next eight questions to assess communicative-critical skills. The statements were rated using a 4-point Likert scale. Functional dimensions are expressed as follows: (4) Never, (3) Rarely, (2) Sometimes, and (1) Often, while communicative/critical dimensions are expressed as (1) Never, (2) Rarely, (3) Sometimes, and (4) Frequently. The mean value of the total scores on the scale being close to 4 is interpreted as a high level of vaccine literacy.[7] Functional vaccine literacy is based on basic literacy skills, and the functional skill dimension is related to reading comprehension. On the other hand, communicative-critical vaccine literacy and the relevant skills are associated with an individual's ability to critically analyze knowledge and use it in life.[7,9,10]

The sample size was calculated based on the information that the population aged 18 and over in Antalya was 2,132,480.[11] The sample, therefore, included 384 participants with a 95% confidence interval (α=0.05), and 410 people were accessed within the specified time. However, 15 participants who declined to participate in the study and 7 participants with missing data were excluded from the study. The study was completed with 388 participants.

Statistical Analysis

Continuous data were presented with mean±standard deviation (SD) or median (min-max) and categorical data with frequency (n) and percentage (%). The normality assumptions were controlled by the Shapiro-Wilk test. The association between categorical data was determined by Pearson chi-square and Fisher's Exact test. The student's t-test was used for comparison of normally distributed numerical data between two groups. One-Way ANOVA was used for the comparison of parametric variables among three or more groups, and the Tukey HSD test was used as a post-hoc test for significant cases. Pearson correlation test was used to examine the relationship between the COVID-19 Vaccine Literacy Scale score and subscales. Multiple linear regression analysis was performed to determine the associated factors with the COVID-19 Vaccine Literacy level of participants. The variables with $p<0.100$ in the univariate analyses were further tested in the multivariate model. Cronbach's alpha coefficient was calculated for the reliability analysis. Statistical analysis was made using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). A two-sided p-value less than 0.05 was considered statistically significant.

Results

Of all the 388 participants in our study, 59.53% (n=231) were female, while 40.46% (n=157) were male. The mean age of the participants was 37.55±14 (18-80) years. Table 1 presents the sociodemographic characteristics and decisions for vaccination of the participants.

The evaluation of the participants according to their sociodemographic characteristics indicated no statistical significance between the mean scores of the scale and its subscales according to age, gender, having a child, history of chronic disease, history of an allergy, and history of a COVID-19 infection. When evaluated according to education level, the vaccine literacy level was found to be significantly higher in the groups formed by university students and university graduates compared to the other groups ($p<0.001$).

Of all the participants, 51.28% (n=199) stated that they had gained enough knowledge about COVID-19 vaccines, and 47.16% (n=183) stated that they thought to have received enough information about COVID-19 vaccines. In addition, 55.41% (n=215) of the participants stated that they found the COVID-19 vaccines safe. The literacy score of the participants who stated that they found the vaccines safe was found to be statistically significantly higher ($p=0.002$).

Table 2 presents the mean scores of the participants received from the scale and its sub-scales in our study, and Table 3 presents the correlation between the scores of the scale and its sub-scales.

Table 1. Sociodemographic characteristics of the participants

Variables	n	%
Age (years), mean±SD / min-max	37.55±14	18-80
18-30	153	39.43
30-40	73	18.81
40-50	94	24.22
50-60	39	10.05
60 and over	29	7.47
Gender		
Female	231	59.53
Male	157	40.46
Educational background		
Primary school	40	10.30
Secondary school	39	10.05
High school	92	23.71
University student	64	16.49
University	153	39.43
Marital status		
Single	196	50.51
Married	192	49.48
Having a child	209	53.86
History of chronic disease	92	23.71
History of an allergy	21	5.41
History of a COVID-19 infection		
No	348	89.69
Yes	40	10.30
Decision for vaccination		
On my own accord	304	78.35
On my family's demand	14	3.60
On my employer's demand	16	4.12
For going abroad	15	3.86
I thought it would be mandatory	39	10.05

Table 2. The participants' mean scores for COVID-19 vaccine literacy

Scales	Mean	SD	Minimum	Maximum	Cronbach's Alfa
Functional score	3.02	0.81	1	4	0.778
Communicative-critical score	2.92	0.71	1	4	0.827
COVID-19 vaccine literacy	2.95	0.54	1	4	0.739

Table 3. Correlation between total scale scores and sub-scale scores

Scales	1	2	3
1. Functional score			
R	1		
P	-		
2. Communicative-critical score			
R	-0.043	1	
P	0.394	-	
3. COVID-19 vaccine literacy			
R	0.465	0.865	1
P	**<0.001**	**<0.001**	-

(Pearson correlation test)

We found the COVID-19 vaccine literacy the highest with a score of 3.11±0.51 in the group who thought they had gained enough knowledge about vaccines, while the mean functional score was statistically significantly lower ($p<0.001$) within the range of 2.86±0.82 in the group who had concerns about the adverse effects of vaccines in the upcoming years (Table 4).

The factors affecting the COVID-19 vaccine literacy score in the participants were evaluated in Table 5 by multiple linear regression analysis. The results showed that as the education level of the participants increased, so did the COVID-19 vaccine literacy ($\beta=0.306$; $p<0.001$) and that the COVID-19 vaccine literacy rate was higher in individuals who voluntarily got vaccinated ($\beta=0.233$; $p<0.001$).

Table 4. Comparison of the scale scores on the basis of the participants' opinions regarding the COVID-19 vaccines

		Functional score		**Communicative-critical score**		**Total score**	
Variables	**n**	**X̄±SS**	**Test value/ p**	**X̄±SD**	**Test value/ p**	**X̄±SD**	**Test value/ p**
I believe that COVID-19 vaccines will be protective							
Yes	252	3.14±0.74	F=8.305	3.02±0.73	F=6.561	3.06±0.52	F=14.238
No	13	2.69±1.12	**p<0.001**	2.77±0.53	**p=0.002**	2.74±0.54	**p<0.001**
Not decided	123	2.81±0.85		2.74±0.66		2.76±0.51	
Significance		*1-2, 1-3*		*1-3*		*1-2, 1-3*	
I think COVID-19 vaccines are safe							
Yes	215	3.14±0.76	F=8.870	2.97±0.76	F=1.434	3.03±0.54	F=6.577
No	21	2.46±1.05	**p<0.001**	2.73±0.63	p=0.240	2.64±0.59	**p=0.002**
Not decided	152	2.92±0.81		2.88±0.66		2.90±0.51	
Significance		*1-2, 1-3, 2-3*				*1-2, 1-3*	
I trust the declarations about COVID-19 vaccines							
Yes	193	3.18±0.75	F=11.266	2.97±0.8	F=1.106	3.04±0.56	F=6.557
No	39	2.56±0.94	**p<0.001**	2.84±0.59	p=0.332	2.75±0.51	**p=0.002**
Not decided	156	2.94±0.8		2.88±0.63		2.90±0.5	
Significance		*1-2, 1-3, 2-3*				*1-2, 1-3*	
I think I have gained enough knowledge about vaccines							
Yes	199	3.23±0.71	F=17.955	3.05±0.74	F=13.862	3.11±0.51	F=30.810
No	79	2.64±0.9	**p<0.001**	2.57±0.69	**p<0.001**	2.59±0.52	**p<0.001**
Not decided	110	2.91±0.79		2.93±0.59		2.92±0.47	
Significance		*1-2, 1-3, 2-3*		*1-2, 2-3*		*1-2, 1-3, 2-3*	
I think that I have been given enough information about vaccines							
Yes	183	3.17±0.73	F=11.369	2.96±0.8	F=0.683	3.03±0.54	F=5.804
No	101	2.71±0.92	**p<0.001**	2.86±0.64	p=0.506	2.81±0.57	**p=0.003**
Not decided	104	3.05±0.76		2.92±0.62		2.96±0.46	
Significance		*1-2, 2-3*				*1-2*	
I have concerns about the unknown side effects of the vaccine in the upcoming years							
Yes	200	2.86±0.82	F=8.285	2.97±0.63	F=2.786	2.93±0.52	F=1.664
No	61	3.22±0.78	**p<0.001**	2.73±0.84	p=0.063	2.89±0.58	p=0.191
Not decided	127	3.18±0.76		2.95±0.75		3.02±0.53	
Significance		*1-2, 1-3*					

(One-way ANOVA with Tukey HSD test)

Table 5. Factors associated with COVID-19 vaccine literacy in participants

	COVID-19 vaccine literacy						95% Confidence Interval	
Model	**B**	**SE**	**β**	**T**	**Sig.**	**VIF**	**Lower**	**Upper**
Educational background	0.121	0.019	0.306	6.371	**<0.001**	1.07	0.084	0.158
Being married	-0.083	0.052	-0.077	-1.598	0.111	1.081	-0.185	0.019
History of COVID-19	0.104	0.082	0.059	1.263	0.207	1.015	-0.058	0.266
Getting vaccinated on his/her own accord	0.304	0.062	0.233	4.933	**<0.001**	1.038	0.183	0.425

($R=0.417$, $R^2=0.174$, $p<0.001$)

Discussion

In this study, which was conducted with the aim of examining the approaches to COVID-19 vaccines in the community and the relationship of such approaches with COVID-19 vaccine literacy, as well as the factors affecting relevant literacy, we found the vaccine literacy status of the participants moderate. The results also implied that the higher the level of education, the higher the literacy and that COVID-19 vaccine literacy was higher in individuals who were vaccinated voluntarily.

The promising results of vaccine applications aimed at limiting the pandemic caused by the SARS-CoV-2 virus have been demonstrated by various studies around the world. A study conducted by Benenson et al. with healthcare workers in a hospital with a high incidence of COVID-19 cases in Israel reported that after two doses of the BNT162b2 vaccine, the number of new cases decreased significantly, indicating that effective vaccination would lead to a safer environment throughout the community.[12] The intermediate results of the Phase-3 study, during which the efficacy of the CoronaVac vaccine in Turkey was evaluated with participants aged 18-59 years, showed that the vaccine had good efficacy for symptomatic SARS-CoV-2 infection and severe course of COVID-19 infection that required hospitalization, and that it has a good safety profile in terms of adverse effects in this population.[13] These situations may contribute to the reduction of concerns about the course of the infection in the community with COVID-19 vaccines.

Another study evaluating the effectiveness of the CoronaVac vaccine in elderly individuals in Turkey, in comparison to younger adults, reported that the administration of two doses of CoronaVac vaccine in the geriatric population with an average age of 78 years was 85.3% effective against the COVID-19 virus, and this rate was 97.4% in the younger group with an average age of 48 years.[14]

Although the positive effects of these vaccines have been demonstrated by studies, negative attitudes towards the acceptance of vaccines and the lack of willingness of individuals to get a vaccine constitute serious obstacles related to immunization.

Around the world, many studies are available to examine approaches to COVID-19 vaccines and their relationship with health literacy, as well as the factors affecting literacy.

In a study evaluating COVID-19 vaccine willingness in Australia before the introduction of vaccines and at a time when the number of cases was quite low, factors such as being female, being younger, having poor health literacy, and lower educational background were directly associated with reluctance to be vaccinated. In the same study, the desire to protect oneself and others were shown as one of the most important reasons for vaccine acceptance.[15] In our study, however, no significant difference was found in the scores on the COVID-19 vaccine literacy scale and subscale groups by age, gender, having a child, history of chronic disease, history of allergy, and history of a COVID-19 infection. Considering the reasons that led people to decide to get vaccinated, it was determined that 78.35% of them decided to get vaccinated voluntarily on their own accord, whereas 3.60% of them decided to get vaccinated upon the request of their families. In addition, 10.1% of the participants in our study stated that they decided to get vaccinated, considering that COVID-19 vaccines would be mandatory in the future.

A study evaluating COVID-19 vaccine hesitancy in the USA has reported that people who believe the vaccine is unsafe to have less knowledge about the virus and are less educated than people who believe the vaccine is safe.[16] In our study, the literacy scores of the participants who stated that they found the vaccines safe turned out to be statistically significantly higher. These situations suggest that low literacy levels may be a significant barrier to trust in COVID-19 vaccines.

Moreover, an online survey conducted in Croatia for the purpose of evaluating the COVID-19 vaccine literacy among people aged 18 and over has indicated that the participants have a moderate level of vaccine literacy with a score of 2.37±0.54.[17] We employed the same scale in our study, in which we found the mean literacy score 2.95±0.54. In addition, the aforementioned study concluded that the level of vaccination literacy increases with the level of education while decreasing with age.[17] Similarly, our study determined that literacy level increased with education level, but no significant difference was found in the scale scores as to age. It is an expected situation that education levels and literacy rates are correlated.

Biasio et al. used online questionnaires in order to evaluate the COVID-19 vaccine literacy of people aged 18 and over in Italy and reported the mean functional score of the participants as 2.92±0.70 and the mean communicative-critical score as 3.27±0.54.[9] In our study, however, the mean functional score of the

participants was 3.02±0.81, which was higher than that of Biasio et al., while the mean communicative-critical score was lower with 2.92±0.71.

In the Turkish validity and reliability study conducted by Durmuş et al., using online questionnaires with the participation of 596 individuals residing in Turkey, the participants' mean score for the COVID-19 vaccine literacy was 2.54±0.56, while it was 2.40±0.75 for functional skills, and 2.60±0.69 for communicative-critical skills.[7] The fact that the mean score of all three groups in our study was higher than that of Durmuş et al. may be related to the fact that our sample consisted of people who presented to COVID-19 outpatient clinics for vaccination, that the majority of them were university students or university graduates, and that the welfare level of Antalya province was relatively higher than some other provinces.

The significance of our research lies in the fact that all data were collected by face-to-face interview technique. In addition, as far as is known, our study is the first to evaluate COVID-19 vaccine literacy in Turkey, apart from the one regarding Turkish validity and reliability.

Our study with 388 participants can be generalized to the population of Antalya province, though it does not give an idea about the extent of COVID-19 vaccine literacy around Turkey, which is the limitation of our study.

In conclusion, although vaccine literacy levels are not considered as low in our study, it should be noted that vaccine hesitancy is not always caused by a lack of knowledge. It should, thus, be acknowledged that individuals may be hesitant due to the unknowns of the pandemic that cannot be predicted even by health authorities, and consequently, vaccination incentive strategies should be developed with the aim of giving society clearer information and confidence rather than fear.

Ethical considerations: Ethical approval was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Antalya Training and Research Hospital as of 24.06.2021 with decision number 9/6.

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Research Article

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EVALUATION OF KNOWLEDGE LEVEL AND APPROACHES OF PHYSICIANS WORKING IN PRIMARY HEALTH CARE INSTITUTIONS IN DENIZLI PROVINCE ON DIABETIC NEUROPATHY

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Abstract

Objectives: Diabetic neuropathy is a complication seen in diabetic patients and involves motor, sensory or autonomic nerve fibers due to minor vessel damage. This study was planned to determine the knowledge and awareness levels of physicians working in family health centers about diabetic neuropathy and their approach to diabetic neuropathy.

Materials and Methods: Our study is a cross-sectional descriptive study conducted in 111 family health centers. Two hundred seventy-nine physicians were included in the study, and 219 physicians (78.49%) agreed to participate in the study. The researchers created the questionnaire form by conducting a literature review. The data were obtained by survey method under supervision.

Results: Of the 219 people participating in the study, 70.78% (n = 155) were male and 6.85% (n = 15) were family medicine specialists. 94.06% of the participants (n=206) gave the optimal glycemic control response as the most effective method to prevent diabetic neuropathy and delay its progression. 74.42% of the participants (n = 163) stated that they did not use any diabetic neuropathy diagnosis and screening tests in their daily practice. 31% (n = 68) of the participants stated that their level of knowledge of diabetic neuropathy was either poor or very poor. 89.49% (n = 196) of the participants stated that they needed training on diabetic neuropathy. Those who rely on their knowledge and clinical experience in diagnosing, monitoring, and treating diabetic neuropathy were 44.29% of the participants (n = 97).

Conclusion: As a result, although the rate of those who correctly knew the primary and secondary prevention of diabetic neuropathy was found to be high among the physicians participating in our study, it was determined that the diabetic neuropathy knowledge level of the participating physicians was insufficient. Simple tests and methods for physicians working in primary care should be included in the daily polyclinic routine.

Keywords: Diabetic neuropathies, diabetes mellitus, knowledge, primary health care.

Introduction

Diabetic neuropathy is the most common chronic complication of diabetes mellitus (DM), affecting different parts of the nervous system, causing different clinical findings related to the peripheral and/or autonomic nervous system, and is associated with the duration and degree of glycemic control.[1,2] Neuropathy causes significant morbidity such as pain, loss of sensation, foot ulcer, gangrene, and amputation.[2] According to the study of the TURNEP working group in our country, diabetic peripheral neuropathy determined by clinical examination affects 40.4% of diabetic patients.[3] If clinical examination and electrophysiological examination methods are added, this rate has been shown to increase to 62.2%.[3]

While it is one of the late findings of Type 1 DM, it can be seen in Type 2 DM patients in the early period, even in the prediabetes period.[4] Since the clinical findings of diabetic neuropathy are similar to other neuropathies, the diagnosis of diabetic neuropathy can be made only after excluding other possible etiologies.[1] Society of Endocrinology and Metabolism of Turkey (TEMD) and the American Diabetes Association (ADA) recommend that patients with type 2 DM should be screened for diabetic peripheral neuropathy every year, and patients with type 1 DM should be screened starting five years after the diagnosis with simple tests (such as 10 gr monofilament) every year.[5,6]

Early diagnosis of neuropathy in diabetic patients and immediate initiation of appropriate treatment are essential in preventing non-diabetic neuropathy, treating symptomatic diabetic neuropathy, and preventing cardiovascular mortality due to diabetic foot and autonomic neuropathy.[5] Tight glycemic control can prevent or delay the progression of diabetic neuropathy. Reducing pain and symptoms of autonomic neuropathy can improve the patient's quality of life.[5]

The lack of an effective treatment for diabetic neuropathy, which is associated with severe morbidity and mortality, highlights preventive medicine. Physicians working in primary health care centers, which constitute the first medical contact point with the health system, should have comprehensive knowledge of diabetic neuropathy and detect diabetic neuropathy in the early period.

This study was planned to determine the knowledge and awareness levels of physicians working in family health centers about diabetic neuropathy and their approach to diabetic neuropathy.

Materials and Methods

Our study is a cross-sectional descriptive study, and it was conducted by including 111 family health centers in Denizli. After obtaining the required permissions, 279 physicians working in family health centers were

included in the study, and 219 physicians (78.49%) agreed to participate in the study (Figure 1). The data of our study were collected between the 10.10.2015-10.12.2015 date range. The data were obtained by survey method under supervision.

The researchers created the questionnaire form to question the sociodemographic characteristics of the participants, their knowledge about diabetic neuropathy, and their professional experience and attitudes by conducting a literature review. The total Cronbach alpha value for the questionnaire on the diabetic neuropathy knowledge level was calculated as 0.916.

11 of the 12 questions questioning the knowledge level of physicians participating in the study about diabetic neuropathy screening, risk factors, clinic, diagnostic method, and treatment contained one correct answer. In the other 1 question, more than one option can be marked, and that question was accepted as correct for those who knew four or more of the eight options. Subgroup analyses were examined by dividing the participants into two groups who gave correct answers to less than six questions and gave correct answers to 6 or more questions. Three questions were used to evaluate their professional experiences in diabetic neuropathy, and four questions were used to evaluate their attitudes.

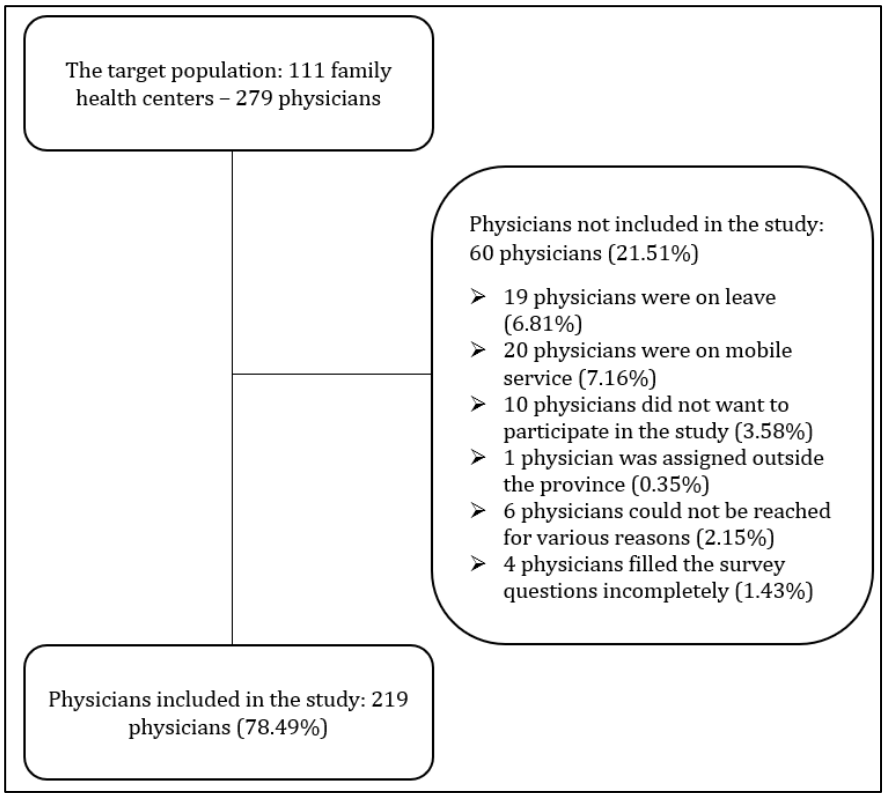

Figure 1. Participants and Non-participants

Statistical Analysis

The conformity of the variables to normal distribution was examined by visual (histogram) and analytical methods (Kolmogorov-Smirnov tests). The numerical data collected in the study are expressed as mean, median, standard deviation, and value range; categorical data are expressed with descriptive methods such as ratio and percentage.

Sociodemographic characteristics were analyzed using Chi-square or Fisher's tests between those with knowledge level scores below six and those with knowledge level scores above 6. Statistical significance was accepted as $p < 0.05$ in the analysis of subgroups. SPSS 22.0 statistical package program was used for analysis.

Results

Of the 219 people participating in the study, 70.77% (n = 155) were male, 6.84% (n = 15) were family medicine specialists, and 88.12% (n = 193) were married (Table 1). The average number of patients enrolled in each physician was 3571.95 ± 607.51, and the average number of patients they looked at in one day was 60.42 ± 17.21.

The questions questioning physicians participating in the study about diabetic neuropathy screening, risk factors, clinic, diagnostic method and treatment, and the percentage of correct answers are given in Table 2.

34.24% of the participants (n = 75) had neuropathy screening from Type 2 DM patients once a year, 21.91% (n = 48) every 6 months, and 9.58% (n = 21) every 3 months, and 32.87% (n = 72) of them never scanned the patients. It was determined that the participants looked at the Achilles reflex at most 20.54% (n = 45), vibration test with 6.39% (n = 14) and pin-prick test with 3.65% (n = 8) in their daily practice. However, it was determined that 74.42% (n = 163) of them did not use any diabetic neuropathy diagnosis and screening tests. Considering the referral attitudes of physicians regarding diabetic neuropathy, 67.12% of the physicians stated their referral criteria as (n = 147) "I refer the patient with DM and typical neuropathy findings", 63.01% of the physicians stated as (n = 138) "if the diagnosis of diabetic neuropathy is suspicious, I refer it", 38.35% of the physicians stated as (n=84) "if clinical findings are atypical, I refer", 20.09% of the physicians stated as (n=44) "I refer every patient I diagnosed with DM".

Table 1. Characteristics of the participants

Sociodemographic data	(n)	(%)	Sociodemographic data	(n)	(%)
Gender			**Marital Status**		
Male	155	70.77	Married	193	88.13
Female	64	29.23	Single	26	11.87
Age			**Average number of patients examined (daily)**		
≤35	17	7.76	≤40	32	14.61
36-45	92	42.01	41-55	61	27.85
46-55	95	43.38	56-70	74	33.79
56-65	15	6.85	≥71	52	23.75
Year in medicine			**Physician's total patient population**		
≤ 10 years	19	8.67	≤ 2000	11	5.02
11-20	85	38.82	2001-3000	22	10.05
21-30	105	47.94	3001-4000	153	69.86
≥ 31 years	10	4.57	≥ 4001	33	15.07
Job title			**Location of the Family Health Center**		
Family doctor	204	93.15	Center	143	65.29
Family medicine specialist	15	6.85	District	76	34.71
Time allocated to diabetes mellitus patients			**Latest diagnosis of diabetic neuropathy**		
1-5 min.	52	23.74	No diagnosis	97	44.29
6-10 min.	115	52.51	0-7 days	54	24.66
11-15 min.	41	18.72	7-30 days	43	19.63
≥ 16 min.	11	5.03	One month and above	25	11.42
Working time in primary care			**Frequency of diabetic neuropathy**		
≤ 10 years	65	29.68	Daily	89	40.64
11-20	91	41.55	Weekly	91	41.55
21-30	55	25.12	Monthly	39	17.81
≥ 31 years	8	3.65	**Education status after graduation**		
			Yes	48	21.92
			No	171	78.08

63.01% (n = 138) of the participants defined their knowledge level about diabetic neuropathy as medium, 31.05% (n = 68) as bad or very bad, 5.93% (n = 13) as good. 45.66% of the participants (n = 100) thought diabetic neuropathy screening, diagnosis, treatment, and follow-up could be made in primary care. 89.49% (n = 196) of the participants stated that they needed training on diabetic neuropathy. Those who rely on their knowledge and clinical experience in diagnosing, monitoring, and treating diabetic neuropathy were 44.29% of the participants (n = 97).

The knowledge levels of women, family medicine specialists, those working in the district, and those diagnosed with diabetic neuropathy within 0-7 days were statistically significantly higher (p; 0.014, 0.046, 0.013, 0.037, respectively) (Table 3).

Table 2. Percentages of correct answers given to the questions questioning the level of knowledge about diabetic neuropathy

Questions	Correct answers	(n)	(%)
1. When is diabetic neuropathy screening done in type 2 DM patients?	Once a year	80	36.52
2. When is diabetic neuropathy screening done in type 1 DM patients?	Once a year	50	22.83
3. When does nerve damage begin in DM patients?	Prediabetes period	43	19.63
4. What is the most important risk factor for diabetic neuropathy in types 1 and 2 DM?	DM and duration of hyperglycemia	192	87.67
5. Diabetic neuropathy (especially distal-symmetrical sensory polyneuropathy involving the lower extremities) is the most important cause of foot amputation, together with infection and ischemia.	True	197	89.95
6. In diabetic neuropathy, the 5th cranial nerve is the most commonly involved cranial nerve and causes facial paralysis, hyperacusis, and a decrease in tears.	False	44	20.09
7. In diabetic neuropathy, the heart becomes overly sensitive to catecholamines. dysrhythmias increased exercise intolerance and sudden death may occur.	True	126	57.53
8. Diabetic neuropathy causes an increase in gastric motility and ejaculation rate and often diarrhea.	False	70	31.96
9. Diabetic neuropathy may be the cause of erectile dysfunction and infertility in men, difficulty in sexual arousal, and dyspareunia in women.	True	197	89.95
10. In diabetic neuropathy, an uncontrolled increase in sweating can be seen in the affected area.	False	40	18.26
11. What is the most effective method to prevent diabetic neuropathy and delay its progression?	Optimal glycemic control	206	94.06
12. Knowledge of diabetic neuropathy diagnosis/screening tests	UK screening test	8	3.65
	Michigan neuropathy screening test	28	12.79
	Pin-prick test	24	10.96
	Achilles reflex	84	38.35
	Monofilament test	10	4.56
	Vibration test (128 hz diapason)	54	24.66
	Determination of vibration threshold (Biotesiometer)	16	7.30
	EMG	133	60.73

Table 3. Knowledge level about diabetic neuropathy

Sociodemographic data	Knowledge level				Statistical analysis
	<6 points		≥6 points		
	Number (n)	Percentage (%)	Number (n)	Percentage (%)	p
Gender					
Male	66	42.38	89	57.42	0.014*
Female	16	25	48	75	
Job title					
Family doctor	80	39.22	124	60.78	0.046*
Family Medicine Specialist	2	13.33	13	86.67	
Workplace					
Center	62	43.36	81	56.64	0.013*
District	20	26.32	56	73.68	
Age					
≤35	4	23.53	13	76.47	0.330
36 - 45	31	33.70	61	66.30	
46 - 55	40	42.11	55	57.89	
56 - 66	7	46.67	8	53.33	
Working time in primary care					
≤10	22	33.85	43	66.15	0.705
11 - 20	33	36.26	58	63.74	
21 - 30	23	41.82	32	58.18	
≥31	4	50	4	50	
Average number of patients examined (daily)					
≤40	10	31.25	22	68.75	0.740
41 - 55	21	34.43	40	65.57	
56 - 70	30	40.54	44	59.46	
≥71	21	40.39	31	59.61	
Average time devoted to DM patients					
1-5 min	26	50	26	50	0.076
6-10 min	37	32.17	78	67.83	
11-15 min	17	41.46	24	58.54	
≥16 min	2	18.18	9	81.82	
Frequency of diabetic neuropathy					
Daily	31	34.83	58	65.17	0.532
Weekly	38	41.76	53	58.24	
Monthly	13	33.33	26	66.67	
The last time to diagnose diabetic neuropathy					
No diagnosis	43	44.33	54	55.67	0.037*
0-7 days	12	22.22	42	77.78	
7-30 days	19	44.19	24	55.81	
One month and above	8	32	17	68	
Education status after graduation					
Yes	17	34.69	32	65.31	0.652
No	65	38.24	105	61.76	

**p<0.05, **p<0.01, ***p<0.001*

Discussion

In our study, 94.06% of the optimal glycemic control response given to the most effective method to prevent diabetic neuropathy and delay its progression shows that the physicians in the study are aware of primary and secondary prevention in diabetic neuropathy. In contrast, more than 50% of physicians working in primary care answered correctly only 5 of the 12 knowledge level questions about diabetic neuropathy in our study. It was found that 74.42% of the physicians did not perform diabetic neuropathy diagnosis/screening tests in their daily practice and the majority of them tend to refer to a higher center. While only 44.29% of the physicians participating in our study rely on their knowledge and clinical experience in diagnosing, monitoring, and treating diabetic neuropathy, 89.49% stated that they need training on diabetic neuropathy.

Many organizations such as the ADA, TEMD, and the Turkish Diabetes Foundation recommend that diabetic neuropathy screening be performed annually in Type 2 DM patients and annually five years after diagnosis in Type 1 DM patients.[5-7] According to the retrospective study conducted by Harris et al. on family physicians in Canada, when looking at the records kept by 29 family physicians participating in the study, it was seen that only 36% of diabetic patients were examined for peripheral neuropathy.[8] In our study, 32.87% of the physicians stated that they never screened for diabetic neuropathy in Type 2 DM patients, while 67.12% stated that they scanned at different time intervals. Only 34.24% of the physicians do the annual screening stipulated by the guidelines.

In the study conducted by Mabrouk et al. in 2013, with 60 family physicians working in family medicine centers in Egypt, it was stated that 48.3% of the participants gave correct answers to 50% or more of the questions, and their knowledge level was considered sufficient.[9] When Peimani et al. conducted a study on diabetes and its complications in Iran in 2010, only 29% of all physicians were sufficient in terms of their knowledge level.[10] 47.8% of the physicians correctly answered the question specifically for diabetic neuropathy.[10] When we evaluate the results we found in our study and the results in the literature, it can be said that the knowledge level of primary care physicians about diabetic neuropathy is low. This situation can be interpreted as a situation that makes the diagnosis, follow-up, and treatment of diabetic neuropathy in primary care difficult.

In our study, the knowledge level score of family physicians who received specialty training was found to be statistically significantly higher than family physicians who did not receive specialist training. This may be because physicians who receive family medicine residency training have more knowledge in rotations and encounter more patients with diabetic neuropathy.

In the study conducted by Mabrouk et al., the knowledge level of family physicians working in urban areas for diabetic neuropathy was found to be better than those working in rural areas, and their practical scores were

found to be lower.[9] The reason why physicians working in rural areas were found to be better than those working in cities in our study and other studies may be that physicians working in rural areas work in a more isolated environment and are not comfortable referring the patient to a specialist. Another reason may be that physicians working in rural areas have to keep their knowledge more up-to-date to combat diabetes complications.[11]

Considering the age and level of knowledge, while the knowledge level score of those younger than 35 years old was 76.47%, it decreased to 53.33% between the ages of 55-66. While the total duration of work in primary care was 66.15% among those who had ten years or less with a knowledge level of 6 and above, this ratio decreased with the increase of working years and decreased to 50% for those who worked for 31 years or more. Accordingly, as the duration of work and the physician's age in primary care increases, there is a decrease in the knowledge level score. However, this decrease in score was not found to be statistically significant between groups for age groups and duration of the study. In the study conducted by Khan et al. among ninety-nine family physicians in Saudi Arabia in 2010, physicians' knowledge, attitude, and practice scores about type 2 DM tend to decrease as the duration of their work increases.[12] According to this study, the knowledge, attitude, and behavior scores of physicians with a working period of 1-5 years were found to be better than physicians who worked longer.[12] The reason for this may be that physicians who receive medical faculty or specialty training are not subjected to any proficiency test after the training process, and the information learned is forgotten as time passes. Another reason may be that young physicians follow the current developments in the diagnosis of diabetes and its complications more closely than more experienced physicians.[11]

It has been determined that more than half of the participants do not trust themselves in diagnosing, monitoring, and treating diabetic neuropathy. The number of DM patients followed only by family physicians in Turkey is unknown. Since diabetic neuropathy is mostly asymptomatic, physicians working in primary care do not consider themselves sufficient in diagnosis, follow-up, and treatment, which may prevent them from screening. Therefore, autonomic system findings of neuropathy requiring expertise may remain untreated for a long time.

It was determined that the physicians in our study had a different approach from the ADA's guideline and mostly preferred to refer DM patients with typical neuropathy findings, although it was not recommended in the guideline. As recommended by the guideline, those who referred patients with atypical clinical findings remained in the minority.

It has been found that physicians working in primary care mostly look at the Achilles reflex in their daily practice. Although the monofilament test is one of the most recommended tests in the national TEMD and ADA

guidelines, only 4.6% of the physicians in our study stated that they knew this test, and only 1.8% applied it in clinical practice.[5,6]

Most of the physicians in our study stated that they agreed with the idea that training in diabetic neuropathy is needed. In the study by Mabrouk et al., 85% of the physicians stated that they needed more information and practice about diabetic neuropathy management.[9] As can be seen from these results, the education given to primary care physicians on diabetic neuropathy should be increased.

We have some limitations to this study. In our survey, a scale was not used for the knowledge level questions, and these questions were prepared by the researchers by scanning the literature. Since the scale was not used, a standard could not be provided in terms of scoring, and this situation made it difficult for us to generalize and make clear statements with our results. Similarly, there is no cut-off point in terms of knowledge level, and therefore, comparison analyzes were made by dividing them into two groups from the midpoint of the total score.

Although diabetic neuropathy is one of the most critical complications of DM, there are deficiencies in the knowledge level about diabetic neuropathy and early diagnosis examination in the primary care physicians in our study. The reason why physicians did not perform screening might be that there is no screening guidance for diabetic neuropathy, unlike the other microvascular complications such as diabetic nephropathy and retinopathy in the "Periodic Health Examinations and Screening Tests Recommended in Family Medicine Practice" published by the Turkish Public Health Institution in 2015 when our study was conducted.

As a result, although the rate of those who correctly knew the primary and secondary prevention in diabetic neuropathy was found to be high among the physicians participating in our study, it was determined that the diabetic neuropathy knowledge level of the participating physicians was insufficient, the majority of them did not perform the diagnostic/screening tests for diabetic neuropathy in their clinical practice, and they tended to refer these patients. Methods that will eliminate physicians' shortcomings in primary care and ensure that they comply with the guidelines should be investigated.

Ethical considerations: This study was initiated with the approval of Pamukkale University Non-Interventional Clinical Research Ethics Committee permission no 16 dated 17.09.2015 and the approval of Pamukkale Provincial Directorate of Public Health. It is declared that the study was carried out in accordance with the Principles of the Declaration of Helsinki.

Conflict of interest: The authors declare no conflict of interest.

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Research Article

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ACUPUNCTURE DECREASES ATTACK FREQUENCY AND IMPROVES DISABILITY IN PATIENTS WITH MIGRAINE WITHOUT AURA: A RANDOMIZED CONTROLLED TRIAL

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Abstract

Objectives: This study investigated the effect of acupuncture treatment on attack frequency, pain intensity, and disability in patients with migraine without aura that received prophylaxis treatment.

Materials and Methods: Eighty-four patients with migraine without aura were randomized to the intervention group (IG; n=42) and control group (CG; n=42). IG received 12 sessions of Acupuncture in addition to prophylaxis treatment. CG received only prophylaxis treatment. The primary outcome measures were monthly attack frequency, duration of attacks and pain severity during attacks. The secondary outcome measure included a change of Migraine Disability Assessment (MIDAS) scores from baseline to endpoints. All participants were followed up for three months.

Results: A total of 80 participants completed the study. There were no statistically significant differences between the IG and CG for either socio-demographic features or the outcome measures at baseline. VAS score decreased from 8.8±0.9 to 3.9±1.5 in IG, while it decreased from 8.7±0.8 to 4.4±2.4 in CG (p=0.001). After three months mean monthly attack frequency decreased from 7.2±3.0 to 3.3±2.3 in IG, while it decreased from 6.3±3.3 to 4.4±2.4 in CG (p=0.040). The mean duration of attacks was 12.1± 2.6 hours before intervention; it decreased to 3.1±1.7 hours in IG (p=0.002). There was a significantly higher proportion of participants in IG who had MIDAS Grade 2 compared to those with CG (42.50% versus 2.50%) at the end of the study (p=0.001).

Conclusion: Acupuncture may be suggested as a complementary treatment option to optimize the clinical management of patients with migraine without aura via decreasing attack frequency and pain severity, also improving disability.

Keywords: Acupuncture, migraine, MIDAS, pain, VAS score.

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Introduction

Migraine is a primary headache disorder that occurs with attacks lasting 4-72 hours, accompanied by photophobia, phonophobia or nausea, and which is unilateral, throbbing recurrent headaches. The current global prevalence of migraine is 10-12%, and it is seen 2-3 times more in women than in men. [1,2] Migraine is one of the important causes of disability-related day loss. Migraine negatively affects the quality of life and mostly creates a cost burden with workday losses due to attacks. [3]

There are several pharmacological treatment options to treat migraine attacks. Non-migraine-specific drugs such as antiemetics, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and migraine-specific drugs such as ergot derivatives and triptans are widely used for treating acute migraine attacks. However, because of relatively few trials that compared the different pharmacological treatment options to treat migraine attacks, comprehensive treatment algorithms are not available. [4,5]

While acute attack treatment is sufficient for some patients with migraine, approximately 40% of patients with migraine require prophylaxis treatment in order to reduce attack frequency, pain severity, and headache-related distress. [6] There are several indications for prophylaxis treatment, such as; having four or more migraine attacks in a month, despite appropriate attack treatment having debilitating attacks, difficulty tolerating or having a contraindication for attack treatment, having a medication-overuse headache, and having attacks with the risk of serious and permanent neurological damage. β blockers such as propranolol, antidepressants and antiepileptic drugs are among the widely used prophylaxis treatment options. [7] However, each drug has its own potential side effects such as fatigue, sleep disorders, nausea and vomiting, and long-term use causes both non-compliance due to side effects and an increase in health costs. Therefore, more and more patients are looking for effective non-pharmacological therapies for preventing migraine attacks. [8]

Acupuncture is a Traditional Chinese Medicine method that has been used for 3000 years to control symptoms, treat illnesses, and relieve pain. [9] Acupuncture is widely used in many countries today as a complementary therapy, especially in cases of chronic pain. Acupuncture is recommended by the NIH (National Institutes of Health) in the treatment of primary headaches. [10] Migraine is one of the diseases in which acupuncture treatment is commonly used. Studies conducted so far have focused more on the effect of Acupuncture on pain intensity in patients with migraine. [11] Data comparing the impact of Acupuncture on both the attack frequency and disability in migraine are relatively scarce. We aimed to investigate the effect of acupuncture treatment on attack frequency, pain intensity, and disability in migraine without aura patients who receive prophylaxis treatment.

Materials and Methods

Study design

This randomized-control trial was carried out between March-September 2018 at Atatürk University Research and Practice Center for Acupuncture and Complementary Therapy Modalities and Atatürk University Medicine Faculty Department of Neurology. The study was performed in adherence to Helsinki Declaration, which is a guideline for clinical trials. The acupuncture treatment was documented in accordance with Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA). The written informed consent form was obtained from all the participants. This study is registered on the website of ClinicalTrials.gov (www.clinicaltrials.gov) with the number NCT04542811.

Participants

In March 2018, a total of 115 migraine patients visited Atatürk University Neurology Outpatient Department. Inclusion criteria were being diagnosed with migraine according to IHS (International Headache Association), receiving migraine prophylaxis treatment, having more than four attacks per month/more than one attack per week, and not having received acupuncture treatment before. Exclusion criteria included being diagnosed with migraine with aura/secondary headache, having received acupuncture treatment for any reason within the last year, not giving consent for acupuncture treatment, and having a fear of needles. It was calculated that a sample of 40 patients for each group provided a statistical power of 80% for determining a difference in VAS score with an error of 5% by the G-power© program. After baseline evaluation by a neurologist, eligible patients (n=84) were enrolled in the study. The secretary in the Neurology Outpatient Department generated a random allocation sequence for the patients who met the inclusion criteria. Eighty-four migraine without aura patients were randomly assigned to the Intervention Group (IG) and Control Group (CG) at a 1:1 ratio. CG received only prophylaxis treatment, while the IG received acupuncture treatment for a total of 12 sessions, three sessions in a week, in addition to prophylaxis treatment. All participants were followed up for three months. The flow chart of the study is presented in Figure 1.

Intervention

Acupuncture points were used without a formal Traditional Chinese Medicine (TCM) diagnosis in the IG. All acupuncture points were selected and localized on the basis of the WHO Standardized Acupuncture Point Location. Acupuncture points selected were bilateral LI-4, LI-11, ST-8, ST-44, SP-6, GB-1, GB-14, GB-20, LR-3, and also GV-14, GV-20. Sterile and single-use stainless steel acupuncture needles measuring 0.25x25 mm were inserted to a depth of 10 mm and retained for 30 minutes without any further stimulation. Acupuncture was

performed by an acupuncturist with an acupuncture practitioner license from the Turkish Ministry of Health. Adverse events were monitored for all acupuncture sessions.

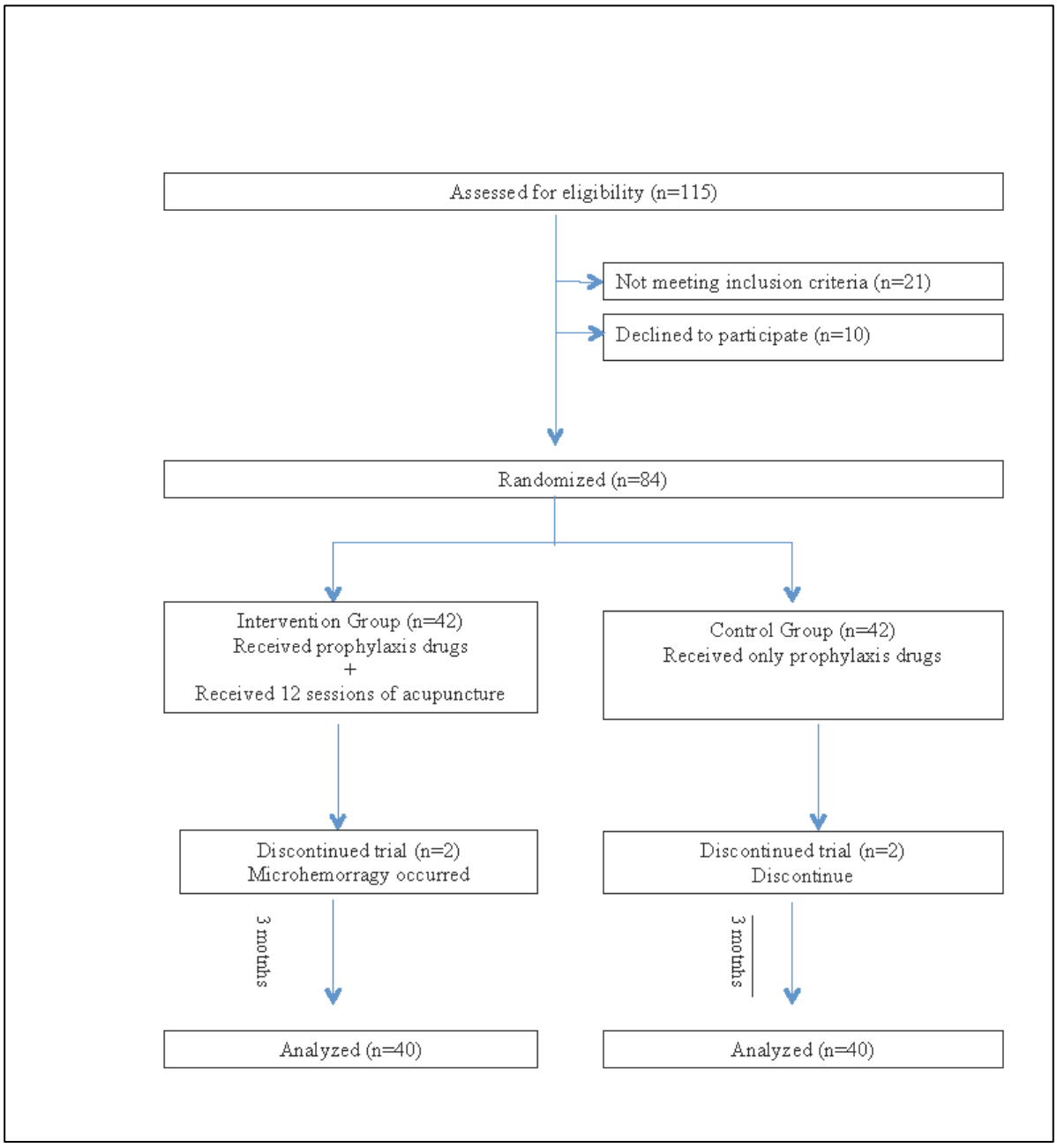

Figure 1. Flowchart of the participants

Outcome measurement

The primary outcome measures were monthly attack frequency, duration of attacks and pain severity during attacks. According to the guidelines of the IHS for Clinical Trials in Migraine, the participants documented each migraine attack day in a month at pain-free intervals of at least 48 hours and durations of the attacks in hours.[12] The pain severity during attacks was measured using a 10-point visual analog scale (VAS). While 0 indicates no pain, ten indicates the most severe pain imaginable.

The secondary outcome measure included a change of Migraine Disability Assessment (MIDAS) scores from baseline to endpoints. The MIDAS questionnaire is an ordinary rating scale to assess the migraine-related disability of a patient with migraine. It is based on responses to five questions about disabilities associated with headaches in the last three months. MIDAS questionnaire has a four-point grading system. Scores ranging from 0 to 5 indicate Grade 1 (little or no disability), scores ranging from 6 to 10 indicate Grade 2 (mild disability), scores ranging from 11 to 20 indicate Grade 3 (moderate disability), and scores 21 or greater indicates Grade 4 (severe disability). Previous studies have demonstrated that the MIDAS is a valid, effective and sensitive tool to assess the disability of migraine. [13] Ertaş et al. performed Turkish validity and reliability of MIDAS. [14] All data were collected at baseline and in the third month.

Statistical analysis

SPSS 23.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Numerical variables are expressed in mean±standard deviation and categorical variables in numbers and percentages (%). Numerical data were analyzed for normal distribution by Skewness. Independent sample t-test and χ^2 test were used to analyze the differences between the groups in terms of outcome measurements. P values <0.05 were regarded as statistically significant.

Results

A total of 115 participants entered the study screening, and 84 participants with migraine who received prophylaxis treatment were randomized. A total of 80 patients completed the study. The mean age of the participants was 37.80 ± 11.70 years. Both IG (n=40) and CG (n=40) had similar baseline characteristics in terms of age, gender, family history, monthly attacks frequency, duration of migraine, and used prophylaxis drug. The baseline characteristics of the participants are presented in Table 1.

Table 1. Baseline characteristics of the participants in each group

Characteristics	IG (n = 40)	CG (n = 40)	P value
Age (year) (mean ± SD)	38.1 ± 12.4	37.5 ± 11.0	0.828
Gender (n,%) Male Female	 7 (17.50%) 33(82.50%)	 5 (12.50%) 35 (87.50%)	0.531
Family history (n,%) Yes No	 19 (47.50%) 21 (52.50%)	 20 (50.00%) 20 (50.00%)	0.823
Monthly attack frequency (mean ± SD)	7.2 ± 3.0	6.3 ± 3.3	0.200
Duration of migraine (year) (mean ± SD)	7.5 ± 6.3	5.5 ± 6.1	0.165
Used prophylactic drug (n,%) Amitriptyline Venlafaxine Flunarizine Others	 8 (20.00%) 5 (12.50%) 12 (30.00%) 15 (37.50%)	 10 (25.00%) 12 (30.00%) 9 (22.50%) 9 (22.50%)	0.169

The comparison of the measurements between IG and CG is presented in Table 2. There were statistically significant differences between the groups as regards VAS score, MIDAS score, duration of attacks and monthly attack frequency at the end of the study. After three months mean monthly attack frequency decreased from 7.20 ± 3.00 to 3.30 ± 2.30 in IG, while it decreased from 6.30 ± 3.30 to 4.40 ± 2.40 in CG (p=0.040).

Table 2. Comparison of the measurements between groups at the beginning and the third month

	IG (n = 40)	CG (n = 40)	P value
VAS (0-10) Beginning Third month	 8.8 ± 0.9 3.9 ± 1.5	 8.7 ± 0.8 4.4 ± 2.4	0.704 *0.001**
Duration of attacks (hour) Beginning Third month	12.1 ± 12.6 3.1 ± 1.7	9.3 ± 8.1 5.2 ± 3.6	0.235 *0.002**
Monthly attack frequency Beginning Third month	 7.2 ± 3.0 3.3 ± 2.3	 6.3 ± 3.3 4.4 ± 2.4	0.200 *0.040**
MIDAS Score Beginning Third month	 39.1 ± 15.1 8.3 ± 9.3	 34.4 ± 15.1 24.9 ± 9.5	0.173 *0.001**

(VAS: Visual Analogue Scale; MIDAS: Migraine Disability Assessment; *p<0.05)

The comparison of MIDAS grades of participants is displayed in Table 3. While the proportion of the grades was similar at the beginning of the study in each group (p=0.745), a significantly higher proportion of participants in IG had MIDAS Grade 2 compared to those with CG (42.50% versus 2.50%) at the end of the study (p=0.001). Conversely, CG was more likely to be in MIDAS Grade 4 (2.50% versus 55.00%, p=0.001) at the end of the study.

Table 3. Distrubion of the MIDAS grades

	IG (n = 40)	CG (n = 40)	P value
MIDAS-1			
Grade 1	None	None	
Grade 2	None	None	0.745
Grade 3	35 (87.50%)	34 (85.00%)	
Grade 4	5 (12.50%)	6 (15.00%)	
MIDAS-2			
Grade 1	14 (35.00%)	None	
Grade 2	17 (42.50%)	1 (2.50%)	*0.001**
Grade 3	8 (20.00%)	17 (42.50%)	
Grade 4	1 (2.50%)	22 (55.00%)	

(MIDAS: Migraine Disability Assessment; MIDAS 1: MIDAS score at the beginning of the study, MIDAS 2: MIDAS score at the end of the study; *p<0.05)

Discussion

The results of this randomized-controlled clinical trial demonstrated that 12 sessions of acupuncture treatment, in addition to prophylaxis treatment, decreased attack frequency in migraine without aura patients. In addition, acupuncture treatment reduces the duration of attacks and pain severity that occurs during attacks and also improves the disability of the patients.

Acupuncture is widely used for the prevention and treatment of migraine attacks not only in China but also in western countries. [15] Clinical studies have shown that Acupuncture as a non-pharmacological treatment is an effective and safe therapeutic method for migraine, at least as a pharmacological treatment. [16] A Cochrane meta-analysis which included 4985 people and 22 studies, indicates that Acupuncture was found to be at least as effective as medication in reducing the frequency of headaches and the number of days that patients experienced migraine attacks and increased the effectiveness of pharmacological treatment. [17] In another study that investigated the long-term effect of Acupuncture applied to migraine without aura; patients determined

that there was a significant decrease in the frequency of migraine attacks. [18] In the present study, while the monthly attack frequency and duration of attacks were similar between the groups before the study, there was a significant decrease in the monthly attack frequency in IG compared to CG. Furthermore, there were observed no serious side effects after acupuncture treatment. The reduction in the frequency of attacks and the duration of pain may also be affected by to decrease in drug consumption. When the side effects and costs of current drug treatments are considered, the direct and indirect cost-effectiveness of Acupuncture as a safe non-pharmacological treatment option is also important in this respect.

Acupuncture is preferred in pain management in most pain clinics today. Approximately one million patients with pain syndrome receive Acupuncture annually in the United States. [19] Studies have shown that patients with migraine have a reduction in pain severity with acupuncture treatment. [20] Wang et al. applied real and sham Acupuncture to 150 patients during migraine attacks, and pain severity was evaluated with VAS scores. The acupuncture group was superior to the sham acupuncture group in relieving pain and reducing acute drug usage. [21] In our study, the severity of pain was measured with a VAS score at the beginning and at the third month. It was found that acupuncture treatment, in addition to prophylaxis treatment in migraine without aura patients, significantly decreased the severity of pain compared to only prophylaxis treatment. The gate control system, nociceptive afferent system and endorphin theories have been found to pain-reducing mechanisms of acupuncture treatment. Besides, our previous study conducted in migraine without aura patients demonstrated that Matrix Metalloproteinase-2 (MMP-2) enzyme activity, which is thought have a role in the pathophysiology of migraine, decreased after acupuncture treatment. [9] Although there are different studies on the analgesic effect of Acupuncture, this mechanism has not been fully clarified yet. The underlying mechanisms of acupuncture treatment in reducing pain severity of migraine require further research.

According to 2017 Global Disease Burden study data, migraine is ranked as the first cause of neurological disorders and the second cause of general disorders in the ranking of years spent with disability in the population of all ages. [22] Migraine attacks not only negatively affect the work and school performances of the patients but also cause a decrease in the quality of life in family and social activities. [23] The Irish Migraine Association reported that migraine affects the performance of the majority of young adults negatively at work or in education, and 39% of these effects are severe. [24] A study conducted in Delhi compared the effects of acupuncture treatment and conventional pharmacological treatment on the psychological profile of migraine patients based on the evaluation of disability parameters. The disability was measured with the MIDAS questionnaire. At the beginning of the study, the quality of life of migraine patients was low, and disability scores were high. At the end of the treatment, it was observed that the acupuncture group showed a better response and therefore was more effective than the pharmacological treatment. Therefore, it was concluded that Acupuncture is a better treatment option than traditional pharmacological treatment not only to relieve migraine pain but also to decrease disability scores of migraine patients. [25] Our findings are in line with all these

researches. In our study, a decrease of close to 80% in mean disability scores was observed after 12 sessions of acupuncture treatment, while it was only 30% in CG.

The severity of migraine can be assessed by determining the grade of disability. MIDAS is reported as easy to use and corresponds to judgments physicians make about disability. [13] MIDAS is widely used to measure disability in three domains: work (school or for pay), household chores, and non-work activities in migraine patients associated with functionality in the last three months. The high grade of MIDAS causes loss of workforce, decrease in production and increase in treatment costs. In our study, there was moderate and severe disability in both groups according to the MIDAS grading system at the beginning. At the end of the study, while most of the patients in the IG had mild disabilities, only 2.5% had severe disabilities. On the contrary, nearly half of the patients in the CG had moderate disabilities, and more than half had a severe disability in the third month. The results of our study indicated that Acupuncture improves the disability status of migraine without aura patients. Reducing disability may also prevent the loss of the workforce.

There are several potential limitations of this clinical trial. Firstly, the sample size in each group was relatively small. Secondly, there was no sham acupuncture group. However, near acupuncture points can be triggered by sham acupuncture. For this reason, adding a sham group is not recommended by some authors. [26] On the other hand, this study demonstrated the effect of our acupuncture prescription on decreased migraine attack frequency and improved disability. Further research is needed to demonstrate how Acupuncture affects migraine attacks frequency and disability.

This study highlights the use of Acupuncture in addition to prophylaxis drugs for migraine without aura patients may optimize the clinical management of the patients. To further confirm this conclusion, additional larger and multicenter randomized-controlled trials with long-term follow-up would be appropriate to address the effectiveness of the acupuncture treatment and the validity of these findings.

Ethical Considerations: The study protocol was approved by the ethics committee of Atatürk University Faculty of Medicine (Date: 29.03.2018, Number: 3/31).

Conflict of Interest: The authors declare no conflict of interest. No financial assistance was obtained for this study.

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ANXIETY, DEPRESSION, AND SLEEP DISTURBANCE IN HEALTH CARE WORKERS TAKING NASOPHARYNGEAL SWAB SAMPLES FOR COVID-19

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Abstract

Objectives: Health care workers (HCWs) fighting COVID-19 are at high risk of transmission. This risk and the increased workload place a heavy burden on HCWs. We aimed to determine anxiety, depression, and sleep disorders in HCWs who form mobile health units (MHUs) assigned to take samples for COVID-19 screening in Rize, Turkey**.**

Materials and Methods: A single-center, a web-based questionnaire was conducted between 20 July - 25 August 2020, in which MHUs on duty with a nasopharyngeal swab sampling were included. Demographic characteristics and information about the MHUs mission and related to the COVID-19 pandemic were collected, and anxiety, depression, and sleep quality were evaluated by Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI) and Pittsburgh Sleep Quality Index (PSQI). One hundred thirty participants were included in the study.

Results: HCWs' median BAI, BDI and PSQI scores were 6, 10 and 5.5, respectively. The frequencies of anxiety symptoms, depression symptoms and sleep disturbances were 45.38%, 53.08% and 50%, respectively. Both the severity and frequency of anxiety and sleep disorders increased as the number of people sampled by healthcare professionals increased and prolonged the working time in the MHUs. Those who suspect they have had COVID-19 at any time and were concerned about transmitting COVID-19 to their family or friends had higher anxiety and sleep quality scores.

Conclusion: In this study, high rates of anxiety, depression, and sleep disturbances were observed in HCWs. Special interventions to protect mental health will be beneficial for HCWs at risk of transmission.

Keywords: Anxiety, COVID-19, depression, mobile health units, sleep disturbance.

Introduction

As a result of COVID-19 disease, which emerged in December 2019 and was described as a pandemic in March 2020, over 433 million confirmed cases and over 5.9 million deaths have been reported globally as of 6 March 2022. In Turkey, from 3 January 2020 to 12 March 2022, there have been 96.094 deaths of COVID-19, reported to WHO.[1,2]

Given its high contagiousness, COVID-19 is characterized by a high risk of infection and even fatal risk among frontline health care workers (HCWs). These risks can create psychological stress for HCWs. There are studies showing a high rate of depression, anxiety and sleep disorders in HCWs in the COVID-19 pandemic.[3,4]

Over one hundred mobile health units (MHUs) have been formed by the Provincial Health Directorate to carry out effective filiation in Rize. During the pandemic process, these teams were assigned to take a nasopharyngeal swab sample (NSS) for COVID-19 screening by going to their homes or workplaces from the specified groups. Hairdressers, restaurant employees, football team managers and players and people who have come from other cities to Rize for tea farming or other reasons were some of the groups screened. HCWs in charge of taking NSS are one of the groups that make the closest contact with the sick person and have a very high risk of transmission if personal protective equipment is inadequate. In addition, this task is carried out at people's homes or workplaces and not in health institutions, which further increases the pressure on HCWs. The aim of this study was to determine anxiety, depression and sleep disorders in HCWs who form MHUs assigned to take samples for COVID-19 screening in Rize, Turkey.

Materials and Methods

Our study was a single-center, cross-sectional, web-based survey study conducted in Rize Province between 20 July–25 August 2020. The study included HCWs working in MHUs who were assigned to take NSS during the COVID-19 pandemic throughout the province. The questionnaire form comprised six parts: online informed consent, demographic characteristics, information about the MHUs mission and related to the COVID-19 pandemic, Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI) and Pittsburgh Sleep Quality Index (PSQI).

The HCWs who wanted to be included in the study were contacted by the researchers. After the people were informed about the study, a link to the web-based questionnaire was sent to the volunteer participants, and they were asked to complete this form completely. Those whose contact numbers could not be reached or who did not volunteer to participate in the study were not included in the study. The questionnaires recorded in the online system were followed up daily, incomplete or repeated questionnaires were checked, and quality control

was carried out. Two hundred and ten HCWs working in 105 MHUs were reached. One hundred and thirty of them volunteered to participate in the study and completed the questionnaire (response rate: 61.9%).

Demographic information like gender, age, marital status, occupation, years of working, and presence of organic and psychiatric illnesses were collected.

Later, information about the MHUs mission and related to the COVID-19 pandemic was questioned. In this section, first, it was determined what role they played in the MHUs (Nasopharyngeal sampling or helpful staff); how many people they took nasopharyngeal samples; how many hours they worked weekly on average, and how long days they had held this task. Afterward, information related to the COVID-19 pandemic was collected. The questions in this section were: "Do you think your protective equipment is sufficient during the sampling?", "Have you ever suspected you have COVID-19?", "Have you ever worried about transmitting COVID-19 to your family or friends?" and "Has any of your family or friends been diagnosed with COVID-19?"

Beck Anxiety Inventory (BAI) is a scale developed in 1988 to measure the severity of anxiety in a psychiatric population.[5] Its Turkish validity and reliability study was conducted by Ulusoy.[6] It comprises 21 items that question subjective anxiety and physical symptoms. Each symptom is graded as none, mild, moderate, and severe, scored between 0 and 3, respectively. Patients are asked to mark the most appropriate expression for each symptom, and the result is obtained by the sum of the items. The cut-off score was set at 16. Scores received by the practitioner; 8-15 = mild anxiety symptoms; 16-25 = moderate anxiety symptoms; 26-63 = severe anxiety symptoms.

Beck Depression Inventory (BDI) was developed in 1961 to measure the behavioral symptoms of depression in adolescents and adults.[7] Its Turkish validity and reliability study was conducted by Hisli.[8] Depression-specific behaviors and symptoms are described in a series of sentences, and each sentence is numbered 0-3. It comprises twenty-one items, and the items are listed according to the mild form to the severe form. Patients are asked to mark the statement that best describes their condition, and the result is obtained by the sum of the items. The cut-off score was set at 17. Scores received by the practitioner; 10-16 = mild depressive symptoms; 17-29 = moderate depressive symptoms; 30-63 = severe depressive symptoms.

Pittsburgh Sleep Quality Index (PSQI) is a scale that provides a quantitative measurement of sleep quality in order to define good and bad sleep in 1989.[9] Its Turkish validity and reliability study was conducted by Agargün.[10] It contains 24 questions. Nineteen of these are answered by the patients themselves. Five questions are answered by the patient's spouse or roommate and are used only for clinical information, and are not included in the scoring. Self-report questions include different factors related to sleep quality. The 18 items included in the scoring are grouped according to 7 component scores. These components are subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleeping medication, and

daytime dysfunction. Each question is evaluated with a number from 0 to 3. The sum of the scores of the seven components gives the total PSQI score. The total PSQI score takes a value between 0-21. If the total score is above 5, it is considered "poor" sleep quality.

The data were analyzed in a computer environment using the SPSS statistical package program. Descriptive statistics were made. The Chi-square test was used for the comparison of categorical variables. None of the numeric variables fit the normal distribution, and the Mann-Whitney U test was used for paired comparisons. The correlation of numeric variables was evaluated by Spearman analysis. Numerical data in the findings were given as median (minimum-maximum), and the frequency of categorical variables was given as the number of people (percentage rate). Statistical significance level accepted as $p < 0.05$.

Results

The characteristics of the participants are shown in Table 1. Ninety-seven (74.62%) of the HCWs were women, and the median age was 30 (21-52) years. While 69 (53.08%) of the HCWs suspected that they had had COVID-19 at any time, 114 (87.69%) were concerned about transmitting COVID-19 to their family or friends. The median BAI score was 6 (0-59). While 41 of the participants (31.54%) had anxiety (BAI≥16), 59 (45.38%) had the least mild anxiety symptoms (BAI≥8) (13.85%; mild anxiety symptoms, 16.15%; moderate anxiety symptoms, 15.38%; severe anxiety symptoms). Participants' median BDI score was 10 (0-46). Depression (BDI≥17) was detected in 38 (29.23%) of the HCWs, while 69 (53.08%) had at least mild depressive symptoms (BDI≥10) (23.85%; mild depressive symptoms, 25.38%; moderate depressive symptoms, 3.85%; severe depressive symptoms). HCWs' median PSQI score was 5.50 (0-18), and poor sleep quality (PSQI score of 6 and above) was found in 65 (50%) of them.

Anxiety frequency and anxiety scores were higher in participants who were female, married, nurses/technicians, had an organic disease, suspected they had had COVID-19 at any time, and whose family or friends had been diagnosed with COVID-19. Anxiety severity and frequency increased with increasing age, years of working, the number of people sampled, and the duration of working in the MHUs (Table 2).

The frequency and severity of depression were higher in women than in men. Depression scale scores were higher in those who suspected they had had COVID-19 at any time. As the duration of work in the MHUs increased, the severity and frequency of depression increased (Table 3).

Table 1. The characteristics of participants

Characteristics	**n (%) or median (min-max)**
Gender	
Male	33 (25.38)
Female	97 (74.62)
Age	30 (21-52)
Marital status	
Married	76 (58.46)
Single	54 (41.54)
Occupation	
Physician/Dentist	29 (22.31)
Nurse/ technician	101 (77.69)
Year of working	7 (1-32)
Organic disease	
Yes	26 (20)
No	104 (80)
Psychiatric illness	
Yes	12 (9.23)
No	118 (90.77)
What role did you take on mobile health units?	
Nasopharyngeal sampling	84 (64.62)
Helpful staff	46 (35.38)
How many people have you taken a nasopharyngeal swab sample? (n=84)	100 (10-650)
How many hours was the weekly working time?	48 (3-90)
How long did you have mobile health units in total? (day) (n=119)	21 (1-150)
Do you think your protective equipment is sufficient?	
Yes	120 (92.31)
No	10 (7.69)
Have you suspected you had COVID-19 at any time?	
Yes	69 (53.08)
No	61 (46.92)
Have you ever worried about transmitting COVID-19 to your family or friends?	
Yes	114 (87.69)
No	16 (12.31)
Has any of your family or friends been diagnosed with COVID-19?	
Yes	30 (23.08)
No	100 (76.92)

Table 2. Characteristics associated with anxiety scores and frequencies of anxiety symptoms

Characteristics	Anxiety score		Anxiety (BAI≥8)	
	median (min-max) or r value	P value	n (%) or median (min-max)	P value
Gender				
Male	2 (0-33)	0.001	8 (24.24)	0.005
Female	8 (0-59)		51 (52.58)	
Age	0.212	0.016	33 (21-52)	0.022
Marital status				
Married	9.50 (0-59)	0.013	43 (56.58)	0.002
Single	5 (0-45)		16 (29.63)	
Occupation				
Physician/Dentist	4 (0-32)	0.014	6 (20.69)	0.002
Nurse/ technician	8 (0-59)		53 (52.48)	
Year of working	0.246	0.005	10 (1-32)	0.006
Organic disease				
Yes	16.50 (0-59)	0.010	17 (65.38)	0.022
No	5 (0-45)		42 (40.38)	
Psychiatric illness				
Yes	8 (0-34)	0.392	6 (50)	0.736
No	6 (0-59)		53 (44.92)	
What role did you take on the mobile health unit?		0.924		0.434
Nasopharyngeal sampling	6 (0-59)		36 (42.86)	
Helpful staff	7 (0-39)		23 (50)	
Number of people taken nasopharyngeal swab sample	0.267	0.014	167.50 (10-650)	0.018
Weekly working time (hour)	-0.066	0.456	48 (8-70)	0.260
Working time in the mobile health unit (day)	0.254	0.005	30 (1-150)	0.030
Do you think your protective equipment is sufficient?		0.330		0.262
Yes	6 (0-59)		53 (44.17)	
No	13 (0-34)		6 (60)	
Have you suspected you had COVID-19 at any time?		<0.001		0.045
Yes	11 (0-59)		37 (53.62)	
No	4 (0-45)		22 (36.07)	
Have you ever worried about transmitting COVID-19 to your family or friends?		0.037		0.080
Yes	7 (0-59)		55 (48.25)	
No	2 (0-45)		4 (25)	
Has any of your family or friends been diagnosed with COVID-19?		0.003		0.024
Yes	16.50 (0-42)		19 (63.33)	
No	5 (0-59)		40 (40)	

Table 3. Characteristics associated with depression scores and frequencies of depression symptoms

Characteristics	Depression score		Depression (BDI≥10)	
	median (min-max) or r value	P value	n (%) or median (min-max)	P value
Gender Male Female	 6 (0-19) 13 (0-46)	<0.001	 8 (24.24) 61 (62.89)	<0,001
Age	-0,041	0.643	30 (22-52)	0.559
Marital status Married Single	 12.50 (0-46) 9 (0-33)	0.380	 43 (56.58) 26 (48.15)	0.343
Occupation Physician/dentist Nurse/ technician	 7 (0-30) 11 (0-46)	0.253	 12 (41.38) 57 (56.44)	0.152
Year of working	0.084	0.340	7 (1-32)	0.229
Organic disease Yes No	 11 (2-46) 10 (0-38)	0.345	 15 (57.69) 54 (51.92)	0.598
Psychiatric illness Yes No	 14.50 (2-32) 10 (0-46)	0.179	 9 (75) 60 (50.85)	0.110
What role did you take on the mobile health unit? Nasopharyngeal sampling Helpful staff	 10 (0-46) 10.50 (0-32)	0.577	 43 (51.19) 26 (56.52)	0.560
Number of people taken nasopharyngeal swab sample	0.093	0.398	150 (10-650)	0.581
Weekly working time (hour)	0.119	0.177	48 (8-90)	0.275
Working time in the mobile health unit (day)	0.367	<0.001	40 (1-150)	0.001
Do you think your protective equipment is sufficient? Yes No	 10 (0-46) 10.50 (4-32)	0.750	 64 (53.33) 5 (50)	0.548
Have you suspected you had COVID-19 at any time? Yes No	 12 (0-46) 9 (0-33)	0.023	 41 (59.48) 28 (45.90)	0.123
Have you ever worried about transmitting COVID-19 to your family or friends? Yes No	 11 (0-46) 7.50 (0-33)	0.097	 63 (55.26) 6 (37.50)	0.182
Has any of your family or friends been diagnosed with COVID-19? Yes No	 15 (0-38) 9.50 (0-46)	0.110	 19 (63.33) 50 (50)	0.199

The frequency and severity of sleep disorders were higher in MHUs with organic diseases. Participants who suspect they have had COVID-19 at any time and were concerned about transmitting COVID-19 to their family or friends had higher sleep quality scores. Anxiety severity and frequency increased with increasing age, years of working, the number of people sampled, and the duration of working in the MHUs (Table 4).

Table 4. Characteristics associated with sleep quality scores and frequencies of sleep disturbances

Characteristics	Sleep quality score		Poor sleep quality (PSQI>5)	
	median (min-max) or r value	P value	n (%) or median (min-max)	P value
Gender Male Female	 4 (0-12) 6 (1-18)	0.100	 14 (42.42) 51 (52.58)	0.314
Age	0.233	0.008	33 (23-52)	0.006
Marital status Married Single	 6 (0-18) 5 (0-17)	0.091	 41 (53.95) 24 (44.44)	0.286
Occupation Physician/Dentist Nurse/ technician	 5 (0-12) 6 (0-18)	0.567	 14 (48.28) 51 (50)	0.833
Year of working	0.287	0.001	10 (1-32)	0.001
Organic disease Yes No	 7.50 (3-14) 5 (0-18)	0.047	 19 (73.08) 46 (44.23)	0.009
Psychiatric illness Yes No	 8.50 (3-16) 5 (0-18)	0.123	 9 (75) 56 (47.46)	0.069
What role did you take on the mobile health unit? Nasopharyngeal sampling Helpful staff	 6 (0-18) 4 (0-17)	0.081	 46 (54.76) 19 (41.30)	0.142
Number of people taken nasopharyngeal swab sample	0.266	0.015	167.50 (20-650)	0.008
Weekly working time (hour)	0.135	0.125	50 (3-90)	0.277
Working time in the mobile health unit (day)	0.343	<0.001	60 (1-150)	<0.001
Do you think your protective equipment is sufficient? Yes No	 6 (0-18) 4.50 (2-16)	0.565	 61 (50.83) 4 (40)	0.510
Have you suspected you had COVID-19 at any time? Yes No	 6 (0-18) 5 (0-12)	0.041	 40 (57.97) 25 (40.98)	0.053
Have you ever worried about transmitting COVID-19 to your family or friends? Yes No	 6 (0-18) 3 (0-11)	0.025	 60 (52.63) 5 (31.25)	0.109
Has any of your family or friends been diagnosed with COVID-19? Yes No	 5.50 (0-18) 5.50 (0-17)	0.683	 15 (50) 50 (50)	1.000

Discussion

As a result of our study, it was observed that 45% of the HCWs in charge of taking NSS for COVID-19 screening in Rize, Turkey had anxiety symptoms; 53% had depression symptoms, and 50% had sleep disturbance. Although we cannot find a similar study conducted on sampling HCWs in the literature, there are studies showing the mental status of healthcare professionals during the pandemic process. The frequencies of anxiety and depression vary in these studies. For example, in a study conducted with over five thousand hospital workers in Wuhan in the first months of the pandemic, the frequency of depression was reported as 14% and anxiety frequency as 24%.[4] In another study conducted in various hospitals throughout China, the frequency of depression was 35%, and the frequency of anxiety was 16%.[11] Anxiety and depression rates are higher in our study, and the findings are very similar to two other studies conducted in China. In these studies, the frequencies of anxiety and depression were determined as 44% and 51%, respectively.[12,13] In a study conducted in a pediatric hospital in Wuhan, where the frequency of anxiety was determined as 9% and the frequency of depression as 25%, poor sleep quality was reported in 39% of HCWs, while in another study involving many hospitals in the Hubei region, 72% of HCWs had sleep disturbance.[3,14] In our study, the rate of sleep disturbance is 50%. Besides the working hours of the participants and the scale cut-off values used, the severity of psychological symptoms may be the reasons for the difference.

In various studies conducted during the pandemic, it has been shown that anxiety, depression, and sleep problems are more frequent and severe in female HCWs.[4, 11-17] Similarly, in our study, psychological symptoms were more frequent in women, and scale scores were also higher (Table 2, Table 3). However, there was no significant difference in sleep quality (Table 4). In previous studies, it has been revealed that depression and anxiety are more common in women than men, and it was emphasized that the differences between the effects of sex hormones and behavioral patterns might cause this.[18-21] In our study, no relationship was found between marital status and depressive symptoms or sleep quality, but anxiety symptoms were found to be more frequent and more severe in married individuals (Table 2, Table 3, Table 4). Considering this aspect, our study contradicts the study of Zhang et al., in which being single was determined as a risk factor for anxiety.[15] When examined, married HCWs were more likely to be concerned about transmitting COVID-19 to family or friends. This situation may have revealed this difference. In a study conducted during the pandemic, it was reported that younger healthcare professionals had less risk of anxiety,[11] in another study, working for over 10 years was stated as a risk factor for anxiety.[4] In another study conducted by Zhang et al., it was stated that having an organic disease in HCWs is a risk factor for anxiety, depression, and sleep disorder.[15] Again, in the study of Zhu et al., an organic disease was expressed as a risk factor for anxiety.[4] In our study, in parallel with these findings, it was observed that anxiety and sleep disorders were more frequent and severe in older, had more years of work and with organic diseases (Table 2, Table 4).

It was observed that the severity and frequency of anxiety and sleep disorders increased as the number of people sampled by healthcare professionals increased (Table 2, Table 4). Depression symptoms were added to this with the prolongation of the working time in the MHUs (Table 3). This result is a clear indication of the pressure that such a risky task creates on healthcare professionals.

As a result of our study, it was seen that almost all the participants thought that their protective equipment was sufficient. However, we found that more than half of them suspect that they have had COVID-19 at any time and that 87% were concerned about transmitting COVID-19 to their family or friends (Table 1). The frequency and severity of anxiety were higher in those who suspected they had COVID-19 (Table 2). In addition, depression and sleep quality scores were also higher (Table 3, Table 4). Anxiety and sleep quality scores were higher in those who reported worrying about infecting their family or friends (Table 2, Table 4). Studies have reported that the concern of being infected or infecting their relatives increases psychological distress and sleep problems.[4, 13, 17, 22, 23] There are studies showing that having COVID-19 positivity in family members or friends of HCWs increases the risk of anxiety and depression.[4,17] Similarly, in our study, the frequency and severity of anxiety were higher in these HCWs than in others.

This study has several limitations. First, study data were obtained from a cross-sectional design conducted over a one-month period. With the fluctuating course of the pandemic, the working tempo of healthcare workers, as well as mental health symptoms, may vary. Therefore, longer-term studies are needed to examine the psychological impact of this sample. Also, causal inferences are difficult to draw because of the cross-sectional design. Second, the participants were selected from HCWs working in Rize Province. Therefore, the findings cannot be attributed to Turkey. There is a need for advanced multi-center studies to be conducted in different geographical regions. Another limitation is that a web-based questionnaire was used for the study to prevent COVID-19 transmission. It is recommended to use clinical interviews in future studies to make psychological evaluations more accurate and comprehensive. In our opinion, the last limitation was the absence of a control group in our study.

The MHUs that are tasked with taking NSS in order to make effective filiation, which is one of the most powerful weapons we have in the fight against COVID-19, are one of the groups that face the highest risk of contact. As a result of our study, high rates of depression, anxiety and sleep disturbances were observed in these HCWs. Protecting the mental health of HCWs is an important component of combating the epidemic. Special interventions to protect mental health will be beneficial for HCWs at risk of transmission, especially women, older people, and those with organic diseases.

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Ethical Considerations: Ethical approval of this study was given by the Non-Interventional Clinical Research Ethics Committee of Recep Tayyip Erdogan University with the decision dated 16.07.2020 and numbered 2020/169.

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

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Research Article

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EVALUATION OF VITAMIN PRESCRIBING BY PHYSICIANS AT A UNIVERSITY HOSPITAL

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Abstract

Objectives: Vitamins are frequently included in physicians' prescriptions. Our study aims to determine the physicians' knowledge about vitamins and nutrition, detect the factors affecting their vitamin prescribing, and gain information about their vitamin prescribing behaviors.

Materials and Methods: Our study included 368 physicians who volunteered to participate in the study. We prepared and used a questionnaire, which consisted of 7 questions about sociodemographic data, 13 questions about nutrition knowledge, 13 questions about physicians' attitudes towards prescribing vitamins, and seven questions about the factors affecting the vitamin prescribing behaviors of physicians.

Results: The most frequently recommended supplements by physicians were vitamin D (62.50%), vitamin C (56.25%), and vitamin B12 (54.89%). Physicians with 11 years or more years in the profession ($p<0.001$) and internal medical sciences physicians ($p<0.001$) gave more correct answers to the knowledge questions. About the frequency of prescribing and recommending vitamins to their patients as supplements, 93 (25.27%) participants said they never did that, 242 (65.76%) said they rarely did that, and 33 (8.97%) said they frequently did that. 90 physicians (24.46%) stated that they prescribed vitamins only upon the patient's request. Only 37 (10.05%) participants considered themselves competent in terms of nutrition knowledge about vitamins. Female physicians used vitamin supplements more ($p<0.001$). Moreover, 305 (82.88%) physicians said that patients who requested vitamin supplements were mostly women.

Conclusion: We found that the majority of our participants gave a negative response to the requests to prescribe vitamins as supplements. Participants considered themselves lacking in nutrition knowledge about vitamins.

Keywords: Vitamins, inappropriate prescribing, physician's role, physicians.

Introduction

Vitamins are the basic organic substances that are necessary for the body and act as catalysts in our body. The prevalence of vitamin use has been increasing all over the world. Vitamins are prescribed to patients for treating deficiencies, and they have commonly used supplements in the absence of deficiencies.[1] Most people may believe that vitamin use is safe, even if the vitamins are not effective. Physicians may also agree to vitamin use by patients who are not diagnosed with vitamin deficiency, saying that "it probably won't help, but it won't hurt either". In addition, studies are reporting that most physicians recommend dietary supplements containing vitamins to their patients, whether they use them themselves or not.[2,3]

While there is a lot of advertising about the potential benefits of vitamins, there is less awareness of their possible adverse effects. Literature reviews about vitamin supplements reveal that some vitamins may even have harmful effects on individuals by increasing the risk of cancer. [4-6] According to some studies, the excessive intake of some vitamins through diet causes toxicity in rare cases. Moreover, the excessive intake of some vitamins in the form of drugs may cause hypervitaminosis.[7,8] In this respect, it is important for public health that physicians provide accurate information to their patients about nutrition. For physicians to successfully fulfill their duties of both providing information to their patients about nutrition and being role models, they must first have sufficient knowledge. At this point, physicians are the ones who will support adequate nutrition, promote the use of appropriate vitamins, and prevent inappropriate use. When physicians promote rational vitamin use and prevent the inappropriate use of vitamin supplements, this becomes an effort toward promoting public health.

Our study aims to determine the physicians' knowledge about vitamins and nutrition, detect the factors affecting their vitamin prescribing, and gain information about their vitamin prescribing behaviors.

Materials and Methods

We conducted our study with physicians working at Trakya University between April and August 2020. A total of 594 physicians working at the Trakya University Faculty of Medicine formed the universe of our study.

We obtained informed verbal consent from the participants and asked them to fill in the questionnaire prepared by the researchers. Working in non-prescribing units (Basic Medical Sciences, Public Health, etc.) was the exclusion criterion. We included 368 physicians that volunteered to participate in the study.

The questionnaire consisted of 40 questions. Seven questions were about sociodemographic data, 13 questions were about nutrition knowledge, 13 questions were about physicians' attitudes towards prescribing vitamins, and seven questions were about the factors affecting the vitamin prescribing behaviors of physicians.

Statistical analysis of the data obtained in the study was performed using SPSS 20 (Statistical Package for the Social Sciences, version 20, serial no:10240642). We employed non-parametric tests in our study because we found that the data from the questionnaire were not suitable for normal distribution.

Descriptive statistics, chi-square analysis test, Mann-Whitney U test, and Kruskal Wallis test were used as statistical methods. Statistical significance level (p) was shown together with the relevant tests and was considered significant when $p<0.05$ and insignificant when $p\geq0.05$.

Results

We conducted this study with the physicians who worked at the Trakya University Faculty of Medicine, wrote prescriptions for their patients, and volunteered to participate in our study between April 1, 2020, and August 31, 2020. We evaluated the data of 368 physicians that answered the questionnaire in full. We found that 54.62% (n=201) of the participants were female, and 45.38% (n=167) were male. The median age was 30 (mean 32.36±6.719) (minimum age 24, maximum age 52).

We evaluated the participants' answers to 13 knowledge questions and saw that the question with the highest correct answer was "Which is the best source of vitamin C?" with 95.11% (n=350). The question with the lowest correct answer was "Which is the best source of B2 (riboflavin)?" with 52.99% (n=195). The median of correct answers was 9 for the 13 knowledge questions.

Table 1 presents a comparison of the correct answers given to the knowledge questions by physicians in terms of gender, years in the profession, work unit, and age. According to this table, the correct answers of the physicians, who worked in the internal medical sciences units, who were older, and who had more than 11 years in the profession, were statistically significantly higher.

We asked the physicians: "Do you prescribe vitamins to patients and/or families who request that you prescribe vitamins as supplements, although vitamin therapy is not required?", two hundred seventy-eight of them (75.54%) answered "no", and 90 (24.46%) answered "yes". When asked about the gender of the patients who requested vitamin supplements, 305 (82.88%) answered "female" and 63 (17.12%) answered "male".

For the question "Do you recommend vitamin supplements when patients do not have a deficiency diagnosis, medical treatment indication, or request?" Ninety-three physicians (25.27%) answered "never", 242 (65.76%)

answered "rarely", and 33 (8.97%) answered "often". Table 2 shows the factors that physicians consider while prescribing vitamins.

Table 1. Comparison of physicians' characteristics and correct answers to knowledge questions

	Answers	n (%)	Median of correct answers	Min-Max	p-value
Gender	Male	167 (45.38)	9	3-13	0.143*
	Female	201 (54.62)	9	4-13	
Years in the profession	Less than a year	36 (9.78)	9	3-11	<0.001**
	1-5 years	202 (54.89)	9	4-11	
	6-10 years	51 (13.86)	9	6-12	
	More than 11 years	79 (21.47)	10	5-13	
Work unit	Internal medical sciences	280 (76.08)	9	3-13	<0.001*
	Surgery	88 (23.92)	8	4-11	
Age	24-30	217 (58.97)	9	3-11	<0.001**
	31-35	68 (18.48)	9	6-12	
	36-40	33 (8.97)	10	5-13	
	41 and above	50 (13.58)	10	8-12	

(n: number of physicians; %: percentage of physicians, Min: minimum, Max: maximum, *Mann-Whitney U; **Kruskal-Wallis)

To the question "Do you give nutrition counseling to patients with a diagnosis of a vitamin deficiency?" 354 (96.19%) physicians answered "Yes" and 14 (3.81%) answered "No".

To the question, "Do you think that you have sufficient nutrition knowledge to be able to give nutrition counseling to your patients about vitamins?" One hundred ninety-six physicians (53.26%) answered "partially sufficient", 135 (36.69%) answered "insufficient", and 37 (10.05%) answered "sufficient". To the question "Do you think that you received sufficient education on vitamins and nutrition in medical school?" 266 physicians (72.29%) answered "No", and 102 (27.71%) answered "Yes".

We found a statistically significant relationship between the physicians' gender and their use of vitamins ($p<0.001$). Female physicians stated that they used vitamins more frequently than male physicians.

We found a statistically significant relationship between the physicians' use of vitamins and their prescribing and recommending of vitamins to patients ($p=0.002$). Physicians who used vitamins regularly and every day had a significantly higher rate of recommending supplements ($p=0.002$).

Table 2. Distribution of considerations when prescribing vitamins

	Most important		Important		Less important		Least important		Total	
	n	%	n	%	n	%	n	%	n	%
Efficacy	252	68.48	55	14.94	16	4.35	45	12.23	368	100
Possible side effects	25	6.80	192	52.17	127	34.51	24	6.52	368	100
Cost	26	7.07	76	20.65	155	42.12	111	30.16	368	100
Brand	65	17.66	45	12.23	69	18.75	189	51.36	368	100

Discussion

The use of vitamins as supplements has become widespread in our daily practice due to media advertisements and patients' requests. A study reporting the trends in dietary supplement use among U.S. adults with the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2012 found the use of supplements to be 52%.[1] In the same vein, according to NHANES data, multivitamin-mineral products were the most frequently used type of supplement at 31%.[9] The use of supplements varies in European countries. For example, studies found that it was common in Denmark and Germany (59% and 43% of the adult population, respectively) but less in Spain and Ireland (9% and 23%, respectively).[10]

A study found that the most used supplement group in our country consisted of vitamins and vitamin-mineral complexes.[11] In a study conducted in Yalova, 50% of participants stated that they used vitamins because a physician recommended them.[12] In our study, 65.76% of the physicians stated that they rarely prescribed and recommended vitamin supplements to their patients, 25.27% never did that, and 8.97% frequently did that. When asked whether they prescribed vitamins to patients and/or families who requested prescriptions for vitamins as supplements, even though vitamin therapy was not required, 75.54% of the physicians answered "no". With these results, we determined that the majority of the physicians participating in our study rarely prescribed and recommended vitamins except for treatment.

Rational drug use is the planning, implementation, and monitoring process that ensures the safe, effective, appropriate, and economical administration of drug therapy. The majority of the physicians in our study stated that they responded negatively to patients' requests for prescriptions for vitamin supplements, and they rarely prescribed or recommended vitamin supplements. In this case, we can say that the physicians acted in line with

rational vitamin use. We determined that the factors that physicians considered most when prescribing vitamins were efficacy and brand. It seems that brand perception affects even the physicians' behavior.

One of the key strategies for promoting a healthy and balanced diet in society is to advocate for healthy nutrition through health care services. Physicians play an important role in this care. In our country, the number of studies on the nutrition knowledge levels of physicians is insufficient. Özçelik and Süroğlu conducted a study in Ankara in 2000 to determine the nutrition knowledge of physicians and found nutrition knowledge levels of 5.33%, 82.34%, and 12.33% of physicians were good medium, and insufficient, respectively.[13] Again in Ankara in 2007, Özçelik et al. conducted a study to determine the nutrition knowledge of physicians in Turkey and found that the nutrition knowledge level of 60.0% of the physicians was mediocre, that of 33.8% was poor, and that of 6.2% was good.[14] In our study, physicians gave correct answers to an average of 9 questions out of the 13 knowledge questions about vitamins. Our participants had a high rate of wrong answers to the questions regarding sources of B vitamins (except for vitamin B12). In the study by Ozcelik et al., male physicians gave more correct answers than female physicians, physicians over 41 years of age gave more correct answers than younger physicians, and physicians with 21 or more years of experience gave more correct answers than physicians with fewer years of experience.[14] Similarly, in our study, physicians over 36 years of age and physicians with 11 or more years of work experience had more correct answers. These results suggest that physicians' experience of vitamin use and nutrition has increased over the years. In our study, internal medical sciences physicians gave more correct answers than surgical unit physicians. This result may be due to differences in clinical practice and education. We can say that physicians working in surgical units have relatively less knowledge of vitamin use and nutrition. Nutrition is a crucial factor in wound healing, and it should be handled more seriously by surgery physicians and supported in education programs. There is a need for more detailed and up-to-date studies on the nutrition knowledge level of physicians in our country. We believe that identifying deficiencies and covering those deficiencies in education will benefit both physicians and patients.

The systematic review by Crowley et al. reported that although medical students wanted to receive nutrition education to develop knowledge, skills, and confidence to counsel patients, they were not supported to provide high-quality and effective nutrition care.[15] Similarly, in our study, physicians were asked, "Do you think that you received sufficient education on vitamins and nutrition in medical school?" and 72.29% of them answered "no". In other words, about three-quarters of the physicians in our study thought that they had not received adequate nutrition education about vitamins in medical school education.

Almost all physicians (96.19%) answered "yes" to the question, "Do you give nutrition counseling to patients with a diagnosis of a vitamin deficiency?". When asked, "Do you think that you have sufficient nutrition knowledge to be able to give nutrition counseling to your patients about vitamins?" 36.69% answered

"insufficient", 53.26% answered "partially sufficient", and 10.05% answered "sufficient". While almost all physicians in our study stated that they gave nutrition counseling to their patients, only 10.05% of them reported that they felt fully competent in terms of nutrition knowledge. In light of the data obtained in our study, it seems necessary to review the vitamin and nutrition education given in medical school education and increase its effectiveness. For the post-graduation period, providing nutrition education about vitamins, both through in-service training and during internships, will benefit both physicians and patients.

There are very few studies in the literature on vitamin use by physicians in our country. A study conducted by Bülbül et al. in Kırklareli found that 67.8% of individuals used vitamins for themselves over the last year.[16] In our study, we found that 17.12% of the physicians had never used vitamins, and 82.88% had used vitamins at least once in their lives. These results suggest that there is a high rate of vitamin use among physicians. In our study, 18.75% of the physicians stated that they used vitamins regularly, and 35.86% of them occasionally. The rate of occasional vitamin use in our study was similar to Coşkun's study, but the rate of regular vitamin use was lower. The reason for this may be that physicians are more conscious than society about vitamin use. In our study, the rate of vitamin use was higher in female physicians than in male physicians in both groups of regular and occasional vitamin use. In the literature, there are studies supporting the notion that women are more interested in vitamin use, and our study indicated similar results.[17]

There are very few studies in the world and in Turkey defining the demographic characteristics of people who use vitamin supplements. The study by Kantor et al. covering U.S. adults from 1999-to 2012 found that women (58%) were more likely to use supplements than men.[1] Similarly, Spencer et al. studied vitamin and mineral supplement use among U.S. medical students and found that women used supplements more commonly and consistently than men.[17] In our study, 83.96% of the physicians answered "yes" to the question of whether patients who requested vitamin supplements were mostly female. Consistent with the literature, the physicians in our study stated that female patients requested more vitamins than male patients. This may be due to the fact that women are more sensitive about health than men.

The study by Dickinson et al., conducted with physicians and nurses in 2007, found that the proportion who recommended supplements to their patients was slightly higher among those who used supplements themselves.[2] In our study, we found that the physicians who regularly used vitamins recommended supplements to their patients, and their proportion was significantly higher than the physicians who never used vitamins. These results suggest that when the physicians used vitamins themselves, they tended to recommend supplements to patients.

According to 2019 data from the Nutrition and Health Survey of Turkey (NHST), the most frequently used nutritional supplements in all age groups were as follows: multivitamin (1.2%) and calcium (1.2%) in the 15-

18 age group; vitamin B12 (2.9%) and vitamin D (2.2%) in the 19-64 age group; and similarly, vitamin B12 (5.5%) and vitamin D (2.8%) in the 65 and over age group.[18] In our study, we found that the most frequently prescribed or recommended vitamin supplements by physicians were vitamin D (62.50%), vitamin C (56.25%), and vitamin B12 (54.89%). We found that the most frequently used vitamins by physicians were vitamin C (35.33%), vitamin D (20.65%), and vitamin B12 (17.39%). According to the NHST, the most frequently used vitamins in society were the ones that were most frequently prescribed and used by the physicians in our study. In our study, we found that, in addition to vitamin B12 and vitamin D, physicians frequently prescribed vitamin C and used it themselves. Bulbul et al. found that the most frequently used vitamins by individuals were vitamin B12 (6.2%) and vitamin C (3.4%), and this finding was similar to our findings.[16] The frequent references to and recommendations of these vitamins on platforms such as social media affect people's preferences and increase demand. In addition, the idea that excessive use is not harmful also increases people's vitamin requests from physicians or pharmacists.

Limitations

Since it was conducted in a single university hospital, the results of the study cannot be generalized to the whole country. The majority of the participants are residents, so different results can be obtained according to the studies to be carried out in the field.

Physicians frequently refer to nutrition and vitamin knowledge in their daily practices. However, the physicians' level of education and knowledge on these issues is not sufficient. While nutrition and vitamin information increase as professional experience increases, the information given on these subjects during medical education is insufficient. In the process of protecting and promoting health, proper and balanced nutrition can only be provided with the competence of physicians. Therefore, it is necessary to eliminate the lack of knowledge immediately, especially in surgical units, in order to meet this need.

Ethical Considerations: We obtained the Ethics Committee Approval through the decision (dated 02.03.2020 and numbered 2020/125) of the Scientific Research Ethics Committee of Trakya University.

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

(Some of the data of our work has been presented in the 20th National Family Medicine Congress, which was held on 11-14 November 2021 online.)

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Research Article

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THE ROLE OF IN VIVO TESTS IN THE DIAGNOSIS OF HYPERSENSITIVITY REACTIONS DUE TO QUINOLONES AND THEIR IMPORTANCE IN CROSS-REACTIONS

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Abstract

Objectives: There are conflicting results regarding the sensitivity of skin tests and cross-reactions between quinolones in quinolone allergy. In our study, we aimed to evaluate the results of skin tests and provocation tests performed with quinolones and to investigate the value of these tests in the diagnosis of hypersensitivity reactions due to quinolones and their usefulness in detecting possible cross-reactions between quinolones.

Materials and Methods: We analyzed the file records of the patients who applied to our clinic for the reason of antibiotic drug allergy and who underwent diagnostic or alternative in vivo diagnostic tests with quinolone group drugs between January 2006 and September 2020. We recorded and evaluated the results of these cases with demographic characteristics such as age, gender, atopy history, concomitant allergic diseases, suspected antibiotic(s), allergic reaction type and time of occurrence, skin tests for diagnosis, and drug provocation tests.

Results: The study included 715 patients, 73.56% of whom were women. Of the patients, 92.72% had a history of early-type drug allergic reactions. Skin tests had been applied to 219 patients. Of the 119 skin tests performed for diagnostic purposes, 48 were positive. A provocation test was performed in 31 of these patients whose skin test was found to be sensitive; 27 of them were negative. In 47 patients, 83 safe cross-over alternative drugs were obtained through provocation tests.

Conclusion: Provocation tests are necessary for the diagnosis of quinolone hypersensitivity reaction and in the evaluation of cross-reactivity. Before provocation tests, evaluation should be made with skin tests.

Keywords: Antibiotics, cross-reactions, hypersensitivity reactions, quinolones.

Introduction

Quinolone group antibiotics are drugs that are effective against gram-negative and positive bacteria. Although generally considered well tolerated, they can cause allergic reactions.[1,2] Quinolones are the second most common class of antibiotics associated with drug-induced allergic reactions. However, the true prevalence of quinolone allergy in the general population is unknown.[3]

Early type (in the first 1-6 hours) or late type hypersensitivity reactions can be seen with quinolones. Immunoglobulin E (IgE) – mediated early reactions (such as urticaria, angioedema, and anaphylaxis) are most common. In cases with a history of hypersensitivity to quinolones, avoiding this drug group is the safest and simplest method.[4] However, if quinolone use is necessary, various tests have been developed to diagnose quinolone allergy. These tests are skin tests (prick, intradermal, patch tests), in vitro (radioimmunoassay (RIA) and the basophil activation test (BAT)) and drug provocation tests. Skin tests and in vitro tests exhibit low sensitivity and specificity. Drug provocation tests, on the other hand, are the preferred gold standard method to confirm quinolone allergy.[5-7]

Evidence for cross-reactivity among quinolones is limited and conflicting. There are no specific rules for predicting cross-reactivity due to quinolones, but studies and case reports have generally reported a high degree of cross-reactivity between first-generation and second-generation agents. In addition, a low degree of cross-reactivity has been reported with third-generation quinolones such as levofloxacin and newer quinolones such as moxifloxacin.[2,4]

Are skin tests less sensitive when the drug is confirmed by provocation tests? In a patient describing a hypersensitivity reaction with a quinolone, can we give another quinolone, or should we restrict the whole group? Additional work is needed to answer these questions.

In this study, we aimed to evaluate the in vivo diagnostic tests (skin tests and provocation tests) and their results performed with quinolones in our clinic and to investigate the value of these tests in the diagnosis of hypersensitivity reactions due to quinolones and their usefulness in detecting possible cross-reactions between quinolones.

Materials and Methods

Study Design and Patient Recruitment

This study was retrospectively planned in Ankara Atatürk Sanatoryum Training and Research Hospital, Allergy and Immunology Department. The study was conducted according to the declaration of Helsinki and

Participants over the age of 18 who applied to our clinic due to antibiotic drug allergy between 2006 and 2020 and who had diagnostic or alternative in vivo diagnostic tests with quinolone group drugs were included in the study.

In the study, 835 patient files were examined. A total of 120 patients were excluded from the study, including 40 patients whose history is unclear / not compatible with drug allergy, 11 patients were tested under antihistamine/corticosteroid/omalizumab treatment, and seven patients did not have a history of antibiotics and drug allergy, were tested for anxiety, and 62 patients whose file information could not be accessed.

Demographic characteristics such as age, gender, atopy history, concomitant allergic diseases, suspected antibiotic(s), allergic reaction type and time of occurrence, diagnostic skin tests and drug provocation tests were recorded from the electronic files of the patients.

The evaluation of drug allergy

In drug allergies, if a true allergy is suspected after taking a detailed patient history, classification should be made according to the duration of the reaction and the type of immune mechanism leading to the findings. Urticaria, angioedema, conjunctivitis, rhinitis, bronchospasm, gastrointestinal symptoms (nausea, vomiting, diarrhea) or anaphylaxis that occur 1 to 6 hours after the first dose of medication are considered early-type (Type 1) drug reactions. Maculopapular eruption (MPE), fixed drug eruption (FDE), toxic epidermal necrolysis (TEN), Stevens-Johnson Syndrome (SJS), etc. that occur after 6 hours are considered as late-type (Type 2, Type 3 and Type 4) drug reactions.[8,9] Afterwards, necessary tests are performed in order to confirm the diagnosis or to obtain alternative medicine. With the information we obtained from the medical records, we classified the type of allergic reaction that occurred with the drug as early-type/late type and recorded in this way.

Skin tests

While performing the skin prick test (SPT), histamine (10 mg/mL) was used as a positive control, and physiological saline was used as a negative control. The prick test was performed with the undiluted form of the drug. If SPT was negative, an intradermal test (IDT) was performed with increasing doses at 20-minute intervals, starting with 1/1000 dilution of the drug and until reaching the maximum non-irritant concentration. The test was considered positive if the diameter of edema in the test area was found to be more than 3 mm compared to the negative control. If the IDT 20th minute readings were negative for delayed reactions, the late readings were evaluated at 24, 48, 72 hours and seven days after the administration of the tests. In the patch

tests performed on the same day as the IDT, drug allergens and control material (the carrier material with which the drug is mixed (example: Vaseline)) were adhered to the patient's skin with a hypoallergenic tape in non-irritant concentrations within the chambers. The test material was removed 48 hours after the test was applied, and the test area was marked and evaluated after 15-20 minutes. Patch test readings were taken on 48th, 72nd (and ±96th hours) and seventh day.

If all skin tests were negative and there were no contraindications, a drug provocation test (DPT) was continued. In our study, SPT, IDT and patch test results of the patients with drugs were found by examining their file records and recorded as negative/positive.

Drug provocation tests

DPT was performed by the oral way in a placebo-controlled, single-blind fashion. The test was started with drug doses ranging from 1/1000 to 1/10 depending on the severity of the reaction in the history. Drug doses were administered at 30-minute intervals until a positive result was obtained or until the daily treatment dose was reached.

If any signs of hypersensitivity related to the skin, respiratory system, cardiovascular system, gastrointestinal system or neurological system occurred during the SPT or during the waiting period predicted according to the history after the test, the test result was considered positive and terminated. In this case, the necessary medical treatment was applied to the patient, and the patient was kept under observation until all findings were resolved. The test was considered negative in patients who could use the last dose of the drug without any problems and did not develop any symptoms during the waiting period. With the information obtained from the patient records, the DPTs performed on the patients were recorded for diagnostic/alternative purposes, and the results were recorded as negative/positive. All drug tests were performed under hospital conditions and in an environment where emergency response conditions were met. Written informed consent was obtained from patients for skin and challenge testing.

Statistical analysis

Predictive analytical software (PASW statistics 18, 2009) was used for the analysis. A type-I error level of less than 5% was used to infer statistical significance. Descriptive statistics were expressed as numbers and percentages for categorical variables and as mean and standard deviation for numerical variables. For categorical variables, in two–group comparisons, the Chi-square test was used when the chi-square condition was met, and the Fisher Test simulation was used when the chi-square condition was not met.

Results

The mean age of 715 patients included in the study was 46±13 years, and 526 were female. The most common accompanying allergic diseases were asthma, chronic urticaria and allergic rhinitis, respectively. Sensitivity to at least one allergen was detected in 83 patients whose allergen sensitivity was investigated by a skin prick test and specific immunoglobulin E (spIgE) (Table 1).

It was determined that the history of allergic reactions due to antibiotics developed primarily due to beta-lactams and secondly to quinolones. Ciprofloxacin in 57 cases, moxifloxacin in 23 cases, and levofloxacin in 15 cases were the most frequently reported quinolone antibiotics. Of the patients, 663 had a history of early-type allergic reactions, and 52 had late-type allergic reactions. The most common early-type drug reactions were anaphylaxis, urticaria and angioedema, respectively, and late-type drug reactions were FIE and MPE (Table 2).

Table 1. Demographic Characteristics of Study Population

Variables	**N: 715**
Age, (year)	46±13
Gender, n(%)	
Female	526 (73.56)
Male	189 (26.43)
Concomitant allergic diseases, n(%)	
Asthma	150 (20.97)
Chronic urticaria	56 (7.83)
Allergic rhinitis	45 (6.29)
Venom allergy	10 (1.39)
Food allergy	7 (0.97)
Atopic dermatitis	6 (0.83)
Atopy, n(%)	
Pollen	47 (6.57)
House dust mite	32 (4.47)
Mold	10 (1.39)
Venom	12 (1.67)
Food	7 (0.97)

Diagnostic drug testing was performed in 220 (30.76%), alternative drug testing was performed in 444 (62.10%) patients, and cross-alternative drug testing was performed in 51 (7.13%) patients.

A total of 656 (91.75%) patients underwent DPT, and 219 (30.63%) skin tests (SPT and/or IDT) were performed. Skin tests were diagnostic in 119 patients, 43 with the responsible drug and 76 with the suspected drug. Among the diagnostic skin tests, SPT was positive in 2 patients, and IDTs were positive in 46 patients. In

these patients, whose sensitivity was determined by skin test measurement, the test was negative in 27 of 31 DPTs performed with the responsible/suspicious drug.

In 47 patients with a history of quinolone antibiotics, DPT tests performed with other quinolone antibiotics were negative. And safe cross-alternative medicine is provided. A total of 83 safe cross-over drugs were obtained with DPTs in 47 patients, 29 patients with a history of ciprofloxacin, nine patients with a history of moxifloxacin, three patients with a history of levofloxacin, five patients with a history of Gemifloxacin, and one patient with a history of ofloxacin (Figure 1a – e). Positivity was detected in the DPTs of 12 patients, which were performed for the purpose of finding alternatives. A significantly higher rate of DPT positivity was observed in women. It was observed that the rate of positivity in SPTs was not associated with concomitant allergic disease, sensitivity to at least one allergen, or the presence of multiple drug allergies.

Table 2. Suspected drugs causing the reaction and observed clinical findings

Variables	**n = 715**
Suspect drug causing drug reaction, n(%)	
Beta Lactam	553 (77.34)
Quinolone	102 (14.26)
Macrolide	86 (12.02)
Azole	30 (4.19)
Sulfonamide	21 (2.93)
Tetracycline	12 (1.67)
Aminoglycoside	2 (0.27)
Unknown	185 (25.87)
Clinical findings observed with drug intake, n(%)	
Urticaria	179 (25.03)
Angioedema	114 (15.94)
Itching	90 (12.58)
Erythema	79 (11.04)
Gastrointestinal symptoms	23 (3.21)
Bronchospasm	19 (2.65)
Laryngeal edema	8 (1.11)
Rhinitis	5 (0.69)
Anaphylaxis	274 (38.32)
Fix drug eruption	29 (4.05)
Maculopapular eruption	19 (2.65)
Stevens-Johnson Syndrome	1 (0.13)
Toxic epidermal necrolysis	1 (0.13)
Drug reaction with eosinophilia and systemic symptoms	1 (0.13)
Vasculitis	1 (0.13)

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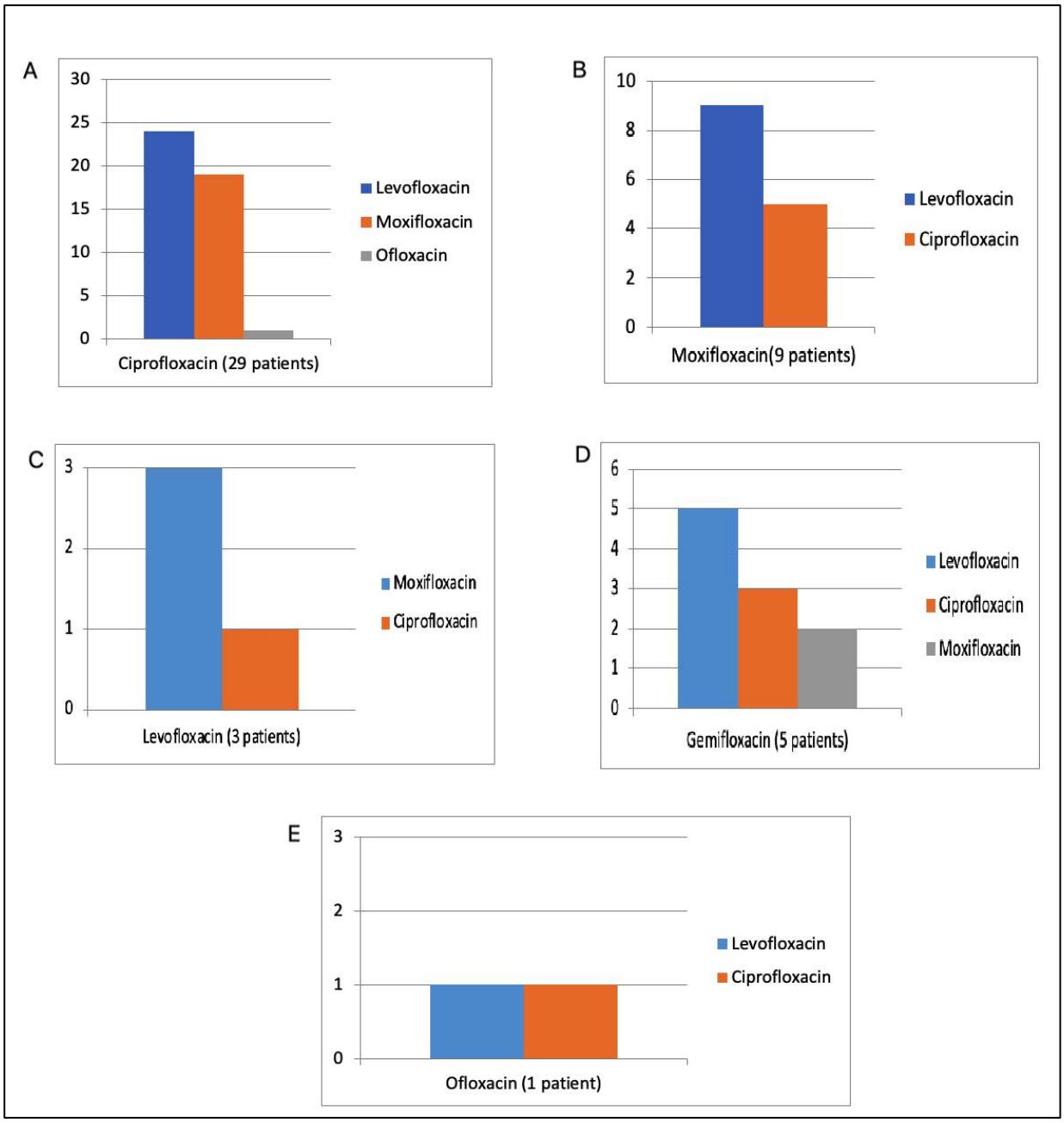

Figure 1. Identification of safe alternatives among quinolones

(A: Negative results on drug provocation tests with levofloxacin, moxifloxacin and ofloxacin in 29 patients describing an allergic reaction to ciprofloxacin. **B:** Negative results on drug provocation tests with levofloxacin and ciprofloxacin in 9 patients describing an allergic reaction to moxifloxacin. **C:** Negative results on drug provocation tests with moxifloxacin and ciprofloxacin in 3 patients describing an allergic reaction to levofloxacin. **D:** Negative results on drug provocation tests with levofloxacin, ciprofloxacin and moxifloxacin in 5 patients describing an allergic reaction to Gemifloxacin. **E:** Negative results on drug provocation tests with levofloxacin and ciprofloxacin in 1 patient describing an allergic reaction to ofloxacin.)

Discussion

In our study, drug reactions were evaluated in 715 patients who presented with a history of early or late antibiotic allergy. As observed in a multicenter study conducted in our country in 2013 evaluating the perception of drug allergy, beta-lactam group antibiotics were found to be the most frequently reported suspicious drugs in our study.[10] Consistent with the literature in our study, quinolone group antibiotics were followed with the second frequency. Although quinolones are generally known to be well-tolerated antibiotics, in recent decades, there has been an increase in quinolone allergy.[2,3,11,12]

Our main aim in our study was to answer the questions of how many of the antibiotic drug reactions evaluated in our clinic were able to perform diagnostic skin tests and provocation tests and whether we could provide safe quinolones as a result of these tests. However, it is a fact that accurate diagnosis of quinolone allergy is not easy due to low sensitivity in skin tests, high probability of false positives and unknown pathogenic mechanisms.[4,13,14] In a study conducted by Eva Perez et al. in which 48 patients were evaluated, it was observed that SPTs had low sensitivity, and IDTs had a high rate of false positive results (88%) due to the irritant and histamine-stimulating effect of the drug. And for this reason, skin tests are considered to be of limited utility for diagnosing quinolone hypersensitivity.[14] In a study conducted by Venturini Díaz et al., in which 71 patients were evaluated by skin tests, ten patients with a positive skin test were given a drug provocation test, and five were positive. A drug provocation test was applied to 34 patients whose skin test was negative, and 32 of them were negative. The skin test results were thought to help predict the provocation test result.[5]

In our study, SPT was found to be positive in 2 patients, and IDTs were positive in 46 patients from the diagnostic skin tests performed on 119 patients. In these patients, whose sensitivity was determined by skin test measurement, the test was negative in 27 of 31 SPTs performed with the responsible/suspicious drug. In a retrospective study by Seitz et al., in which they examined the results of diagnostic tests in quinolone allergy, 89 out of 101 patients had negative skin tests, and when DPT was continued in these patients, quinolone allergy was excluded with a negative result in 71 patients.[15] As can be understood from this, diagnosing drug allergy based on anamnesis often leads to an unnecessary diagnosis of drug allergy. If a true drug allergy is suspected in the patient describing drug allergy after careful evaluation of the medical history, skin tests should be planned according to the clinical findings described first. Patients with a negative skin test should be evaluated with a provocation test. In a study by Demir et al. in which 54 patients with a history of hypersensitivity reactions to quinolones were evaluated, it was observed that the contribution of skin tests to the diagnosis and cross-sensitization was low. For this reason, the necessity of performing a provocation test to identify the culprit or alternative drug was emphasized.[16]

The most frequently accused quinolones in our study were ciprofloxacin, moxifloxacin and levofloxacin, respectively. Although the order of quinolones varies between studies, the most frequently accused quinolones in the literature are ciprofloxacin, moxifloxacin and levofloxacin, respectively, similar to our study.[5,15,17] In another study, the accused drugs were followed as moxifloxacin, ciprofloxacin and levofloxacin, respectively.[7] It is thought that the ranking in this study may be related to their higher consumption in clinical practice compared to others.[3]

Cross-reactions between quinolones are still controversial due to conflicting results among publications. In some publications consisting of case reports and series, a high degree of cross-reactivity has been reported, especially between first-generation agents (nalidixic acid) and second-generation agents (norfloxacin, ciprofloxacin).[6,18] A lower degree of cross-reactivity has been reported in some publications, particularly with third-generation quinolones such as levofloxacin and newer quinolones such as moxifloxacin.[17,19] For the detection of alternative quinolones in this drug group with cross-reaction potential, skin tests can be performed, taking into account the previous reaction type and severity and provocation tests if negative. In our study, as a result of the provocation tests we conducted, we were able to obtain 83 safe alternative quinolones in 47 patients.

One of the limitations of our study is that we could not perform in vitro tests such as specific IgE determination and BAT. Our study is a retrospective study, and these tests are expensive and not applied in clinical routine. Another limitation of ours is that we could not perform a diagnostic test with the responsible drug in more patients. It could be evaluated by an oral provocation test considering the false-positive rate in quinolones with a positive skin test.

As a result, unnecessary diagnosis of drug allergy can be avoided by performing skin tests for quinolone group drugs and provocation tests, if negative, in accordance with the patient's history. In cases where diagnostic tests are hesitant, cross-reactivity can be ruled out by skin tests and if negative, by provocation tests, alternative quinolones can be provided.

Ethical Considerations: Ethical approval was acquired from the Keçiören Training and Research Hospital (Ethics Committee No: 10.11.2020/ 2186).

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Research Article

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LESS KNOWN AND NEGLECTED RENAL COMPLICATION OF PRIMARY HYPERPARATHYROIDISM: RENAL CYSTS

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Abstract

Objectives: Simple renal cysts are lesions that are epithelial in origin, with a prevalence changing between 5 to 15% in the normal population. In animal studies, it was shown that PTH might stimulate cyst formation via intracellular signaling systems triggering epithelial cell proliferation. Our primary aim was to detect the simple cyst prevalence in a large cohort of PHPT and compare it with sex and age-matched health individuals. The secondary aim was to detect determinants of cyst formation in PHPT.

Materials and Methods: A total of 307 PHPT patients and 112 healthy controls were enrolled in our study. PHPT group was compared with the control group regarding the biochemical parameters and presence, size and bilaterality of renal cysts in the US performed by a single experienced radiologist.

Results: Prevalence (43.65% vs 25%, p=0.020) and size [28.40 mm (min-max: 4-82) vs 12.20 mm (min-max: 3-94) (p=0.013)] of simple renal cysts were higher in the PHPT group compared to controls. The presence of renal cysts was correlated with age but not sex and positively correlated with the serum PTH level in regression analysis. Serum Ca, P, and 24-hour urinary Ca excretion were not found to be associated with cyst formation.

Conclusion: Simple renal cysts are a benign renal complication of PHPT that does not alter renal function significantly, and their presence is directly correlated with the hypersecretion of PTH.

Keywords: Simple renal cyst, parathyroid hormone, complication, primary hyperparathyroidism.

Introduction

Simple renal cysts are lesions that are epithelial in origin with a thin wall and filled with fluid.[1] As reported before in different series, they occur in 5.20-15.20% of the population.[2] Simple kidney cysts are very common as people begin to age; up to half of all people, 50 years of age and older have at least one kidney cyst.[3,4] It is important to differentiate simple cysts from atypical or complex cysts, which may be cystic tumors and various infectious and inflammatory lesions.[5] Most of the time, they don't cause any symptoms and are diagnosed coincidentally by ultrasound ordered for an unrelated reason. Rarely may they become symptomatic if they rupture and cause bleeding.[6] Other rare complications are infections, mass effects on the other organs, and increased blood pressure.[7]

Primary hyperparathyroidism (PHPT) is a common endocrine disorder that is characterized by hypercalcemia and elevated or inappropriately normal serum levels of parathyroid hormone (PTH).[8] In recent years, most of the cases are asymptomatic with mild hypercalcemia detected during routine biochemistry tests. The common complications due to PHPT are osteoporosis, hypercalciuria, decreased renal function and nephrolithiasis.[9] There are also less pronounced complications such as the increased risk of cardiovascular disease, higher than normal frequency of diabetes and obesity, and hyperuricemia. [10,11]

In some in vitro and in vivo models, it is suggested that PTH plays a role in the development of renal cysts. In fact, PTH has been demonstrated to stimulate kidney cell proliferation in vitro by activating the mitogen-activated protein(MAP) kinase intracellular signaling.[12,13] In addition, PTH was demonstrated to activate the proliferation of the epithelial cells of the renal tubules harboring mutations of the PKD1 gene that takes part in autosomal dominant polycystic kidney disease.[13]

In this study, our primary outcome was to compare the renal cyst prevalence of PHPT patients who were recommended to undergo surgery regarding indications in the international guidelines and compare it with age and sex-matched healthy controls. Our secondary aim was to detect determinants of cyst formation in PHPT.

Materials and Methods

A total of 307 patients with PHPT who were admitted to our outpatient clinics between the dates of May 2015-April 2020 with PHPT and evaluated in the multidisciplinary council, including the surgeons, nuclear medicine specialists and endocrinologists, having at least one indication for surgery, were enrolled in this study. Informed written consent was obtained from all subjects prior to their enrollment, and our local ethics committee approved the study protocol in accordance with the principles of the Declaration of Helsinki. Age

and sex-matched 112 healthy controls without any known previous kidney or endocrinologic disease were chosen as the control group. Patients who were under the age of 18, without a definitive diagnosis of PHPT and hypercalcemia, and taking drugs that may cause hypercalcemia, such as lithium or thiazide diuretics, were excluded. Diagnosis of PHPT was made by the concomitant presence of high serum levels of albumin-corrected calcium and elevated or inappropriately normal PTH levels. Familial hypocalciuric hypercalcemia was excluded in all patients by the measurements of 24 hours-urinary calcium excretion, fractionated calcium excretion and Ca SR inactivating mutations if required.

The normal range of calcium, according to our hospital's assay, was (8.80–10.20 mg/dL) (Roche Diagnostics, Manheim, Germany). Plasma intact PTH was measured using the Allegro immunoradiometric assay (Roche Diagnostics, Manheim, Germany). The detection limit of the assay was 1 pg/mL (normal range, 10–65 pg/mL), and the intra- and interassay coefficients of variation were 2% and 10%, respectively. In all individuals, we calculated albumin-adjusted calcium by using the following equation (Ca+(4-serum albumin) x0.80). Vitamin D was measured by liquid chromatography coupled with tandem mass spectrometry (Schimadzu-API LC-MSMS API 3200, Canada). The lower and upper detection limits were 4 and 150 μg/L, respectively.

Patients had an abdominal ultrasound (US) performed by a single experienced radiologist. Each US was performed with a low-to-medium frequency (3.50–5 MHz, depending on the physical characteristics of the subject) convex probe and the ultrasound scanner (Hitachi, Japan). Ultrasonography was performed in the supine, right and left lateral decubitus positions. The presence, number, and position of cysts and stones were evaluated.

BMD was performed using dual-energy X-ray absorptiometry (DXA) of the lumbar spine and the proximal femur in posteroanterior projection. At the time of the study, there was a Hologic DXA scanner within the center. The least significant change (LSC) used in the MBC was 4.50%, both for the spine and hip and distal radius.

Statistics

Descriptive statistics were defined as the number (n) and percentage (%) for categorical variables. For continuous variables, mean and standard deviation (SD) were used to describe normally distributed variables and median with minimum and maximum values were used for non-normal distributions. Participants were categorized as those with or without PHPT. Between-group differences in continuous variables were assessed by unpaired student's t-test or Mann-Whitney U test, as appropriate. Between-group comparisons in categorical variables were assessed by the $\chi 2$ test or Fischer's exact test. SPSS 23.0 for Windows (IBM Corp., Armonk, NY) was used for the analyses. Multivariate analysis was performed by multiple regression analysis for the factors influencing the presence of kidney cysts.

Results

A total of 307 patients with PHPT and sex and age-matched 112 healthy controls were enrolled in the study. The median age of PHPT and control groups were 55 (26-78) and 56 (20-82) years, respectively (p=0.070). Number and percentage of female/male patients in PHPT and control groups were 274 (89.25%)/33(10.75%) and 99 (88.39%)/13 (11.61%), respectively. Number of patients with/without renal cysts in the PHPT group was 134 (43.65%)/173 (56.40%) vs 28 (25%)/84 (75%) in the control group (p=0.020). Among the patients with PHPT, 32 had unilateral, whereas 102 had bilateral cysts. In the control group, seven patients had unilateral, and 21 patients had bilateral simple renal cysts. There was no significant difference between the groups regarding bilaterality. The median size of the renal cysts was 28.40 mm (min-max:4-82) in the PHPT group, whereas it was 12.20 mm (min-max:3-94) in controls (p=0.013). Serum TSH and creatine were comparable between groups, whereas median Ca and PTH were significantly higher in PHPT compared to controls (p<0.001). Serum P was significantly lower in the PHPT group compared to controls (p=0.030) (Table1).

Table 1. Biochemical and clinical data of the patients with PHPT and healthy controls

	PHPT (n=307)	Controls(n=112)	P value
Female/male (n/%)	274(89.25%)/33(10.75%)	99(88.39%)/13(11.61%)	0.980
Median age (min-max) (years)	55 (26-78)	56 (20-82)	0.070
Presence of renal cysts (n/%)	134(43.65%)	28 (25%)	0.020
Unilateral/bilateral cysts(n)	32/102	7/21	0.940
The median longest diameter of the cyst (min-max)	28.40 (min-max:4-82)	12.20 (min-max:3-94	0.013
TSH (mean)	2.23±1.56	1.89±0.90	0.023
Ca mg/dl (mg/dl)	11.47±1.08	9.08±0.84	<0.001
P mg/dl (mg/dl)	2.74±1.12	3.73±0.95	0.030
PTH pg/ml (median)	225 (67-876)	40(27-92)	<0.001
Albumin g/L	4.42±0.92	4.36±1.03	0.570
Creatine mg/dl	0.88±0.22	0.91±0.27	0.470

(Ca: Calcium, P: Phosphorus, PTH: Parathormone)

In the PHPT group, 298 (97%) of 307 patients underwent surgery in our center. Histopathology was reported as parathyroid adenoma in 293(98.30%), parathyroid hyperplasia in 3(1%) and parathyroid carcinoma in 2 (%0.70). Median Ca excretion in 24 hours urine collection was 357 mg/day (min-max;114-1216). Median P excretion was 740 mg/day (min-max;1-2160) (Table 2).

BMD was documented for everyone in the PHPT group but not in the control group. Of 307 PHPT patients, 54 had osteopenia, 77 had osteoporosis, and 176 had normal T scores at one of three sites in DEXA. Kidney stones were detected in 70 of 307 PHPT patients and in 4 of 112 control individuals. The difference between the two

groups was statistically significant (p<0.001). The presence of renal cysts in PHPT patients with or without nephrolithiasis was similar (p=0.475)

In the regression analysis, parameters associated with the presence of renal cysts were found to be age and serum PTH level. Neither serum calcium nor urinary Ca excretion was not associated with cyst formation (Table 3).

Table 2. Renal and bone-related parameters and prevalence of complications in PHPT group

24 hours urinary Ca (mg/day)	357 (114-1216)
24 hours urinary P (mg/day)	740(1-2160)
Osteoporosis (n/%) Osteopenia (n/%) Normal T score(n/%)	54 (17.59%) 77 (25.08%) 176(57.33%)
Nephrolithiasis present/absent(n/%)	70 (22.80%)/237(78.20%)

(Ca: Calcium, P: Phosphorus)

Table 3. Multiple regression analysis for the detection of risk factors for the presence of simple renal cysts

	P value	Odds Ratio
Age	<0.001	0.270
Serum total Ca	0.580	0.044
Serum PTH	<0,001	0.310
Serum P	0.570	-0.016
24 hours urinary Ca	0.693	0.032
24 hours urinary P	0.815	-0.410
Sex	0.720	-

(Ca: Calcium, P: Phosphorus, PTH: Parathormone)

Discussion

PHPT is a common endocrine disease that occurs because of the autonomous secretion of PTH and resultant high Ca levels and lack of feedback inhibition due to a reduced number of calcium-sensing receptors (CaSR). The prevalence is 7 per 1000 people, and it is 3-4 times more frequent in females than males.[14] In the last decade, the vast majority of PHPT cases have been admitted to outpatient clinics with mild or nonspecific symptoms.[15] In our study %42 PHPT patients had either osteopenia or osteoporosis, and %22 had symptomatic or asymptomatic nephrolithiasis detected with US.

In this study, we detected that the renal cyst prevalence was significantly higher in PHPT patients compared to healthy controls. It was also detected that the main determinants of cyst formation were age and PTH level. Although renal cysts are benign, harmless lesions in most cases, they may lead to serious complications such as rupture and bleeding rarely and can be accepted as end-organ damage of primary hyperparathyroidism, according to our results.

The major renal manifestations of PHPT are hypercalciuria related to impaired renal function and nephrocalcinosis. Symptomatic kidney stones were reported to occur in %20 of the cases, whereas nephrocalcinosis is rare.[16] In asymptomatic PHPT presence of asymptomatic kidney stones detected with conventional imaging such as US or non-contrast CT is considered an indication for surgery. Therefore, it is recommended in the guidelines to screen all PHPT patients with US.[17]

Herein the present study, our aim was to reveal another unpronounced renal complication that may be related to PHPT, which is a "simple renal cyst". To our knowledge, there is only one study without a control group in the literature.[12] In our study, we detected that the prevalence and the size of the simple renal cysts were significantly higher than the age and sex-matched healthy individuals. In the previous study, renal cyst prevalence was found to be 34.90% in PHPT patients, which was slightly higher than our population, which might be due to older mean age.[12] The limitation of the mentioned study was its retrospective nature, including US examinations by different operators and the lack of a control group.

In our study presence of simple cysts was not associated with gender in the PHPT group in contrast with the general population, where male gender is a well-known risk factor.[4] In our study number of female patients was eight times higher than males, which means increased PTH is a risk factor for the formation of simple cysts regardless of sex.

In the regression analysis, determinants of cyst formation in the PHPT group were age and serum PTH but not serum Ca, P, or 24 hours urinary excretion of Ca. In addition to that, prevalence did not differ in patients with or without kidney stones. PTH activates the intracellular pathways by binding to transmembrane Gs/adenylyl cyclase and Gq/phospholipase C and in the proximal tubule-like opossum kidney cell line. In addition to that, PTH causes PKC- and PKA-dependent inhibition of Na-dependent phosphate (Na/Pi) transport.[13] Adding to its well-described regulation of renal transport function, several findings suggest that PTH may regulate MAPK in target tissues.[18] In one study, PTH caused time- and concentration-dependent increases in MAPK activity that resulted in increased proliferation of mesangial and tubular epithelial cells.[19] In light of those findings, we can conclude that PTH is responsible for cyst formation by increasing the cellular growth of epithelial cells in the kidneys. In our study, the median largest diameter of the cysts was higher in PHPT compared to controls supporting the findings of Corbetta et al.[12]

In the PHPT group, all cysts were reported as simple cysts. That finding supports this possible complication of PHPT is relatively benign and can cause less morbidity when compared to other renal complications such as stones, reduced GFR and nephrocalcinosis. However, several observational studies have reported that the incidence and prevalence of hypertension are higher in patients with simple renal cysts, which means that benign complications may worsen cardiovascular outcomes and renal functions in PHPT patients. [20,21,22]

There are a few limitations in our study. We included only PHPT patients with surgery indications since their information was recorded in the database of the multidisciplinary council. PHPT patients with an asymptomatic and mild form of the disease without any indication for surgery were not included. Since patients with an indication for surgery might have more severe diseases, that may have caused a bias. Another limitation is the relatively smaller sample size of the control group, which is nearly 1/3 of the patient group. That was due to difficulty in finding age-matched healthy individuals undergoing renal ultrasonography.

In conclusion, simple renal cysts are benign renal complications of PHPT that do not alter renal function significantly, and their presence is directly correlated with the hypersecretion of PTH. They can rarely cause complications and lead to misdiagnosis of hereditary polycystic kidney disease.

Ethical Considerations: Approval was obtained from Ankara Yildirim Beyazit University Faculty of Medicine Clinical Research Ethics Committee for the study (Decision number: 32 Date: 17.03.2021).

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

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THE ASSOCIATION BETWEEN SLEEP AND QUALITY OF LIFE IN PATIENTS DIAGNOSED WITH SUBCLINICAL HYPOTHYROIDISM

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Abstract

Objectives: Thyroid disorders are frequently associated with sleep problems, and quality of life is adversely affected at the same time. The purpose of this study was to determine the effect of sleep problems on quality of life in patients with subclinical hypothyroidism (SH).

Materials and Methods: This descriptive, cross-sectional study was performed with patients presenting on an outpatient basis to two separate clinics in the internal diseases department of a training and research hospital between February and July 2021. The study population consisted of 103 patients. p values <0.05 were considered significant.

Results: The mean age of the participants was 44.46±14.12 years, and the mean duration of disease was 7.01±4.90 years. The participants' total Rolls Royce Quality of Life score mean was 104.99±18.48, and the mean PSQI total score was 7.11±3.75. A moderate negative correlation was observed between the participants' mean Pittsburg Sleep Quality Index and mean cognitive function, social relationships and quality of life scores. According to the linear regression analysis performed to examine the effect of sleep quality on quality of life, 10% of the change in the quality of life is explained by sleep quality.

Conclusion: In this study, the quality of life of the participants was below moderate, and it was determined that the impairment of sleep quality adversely affected the quality of life. Since sleep quality affects the quality of life in patients followed up with subclinical hypothyroidism, sleep assessment is recommended. In addition, it is recommended to take initiatives to increase sleep quality and to investigate different factors affecting the quality of life.

Keywords: Quality of life, sleep, subclinical hypothyroidism.

Introduction

Subclinical hypothyroidism (SH) is defined as the presence of high levels of thyroid-stimulating hormone (TSH) together with normal free triiodothyronine (fT3) and free thyroxine (fT4) levels in serum.[1] It is more frequently seen in women and with advancing age, with a prevalence of 18% being reported in community studies.[2] SH has been linked to increased cardiovascular diseases.[3,4] It can also involve non-specific symptoms such as fatigue, depression, malaise and cognitive impairment.[5,6]

Thyroid disorders are frequently associated with sleep problems[7] and sleep quality. Sleep can affect hormone secretion, and endocrine function disturbance can also have an impact on sleep. There are two processes that link sleep and endocrine functions. These are the circadian rhythm and sleep/wakefulness status, both of which affect hormone secretions. Adrenocorticotropic hormone and cortisol are hormones regulated by the circadian rhythm, and the release of growth hormone is essentially regulated by sleep/wakefulness status.[8,9]

Sleep problems adversely impact the quality of life and health behaviors.[10] The cause of the impairment of quality of life in patients with a thyroid disorder and the effect of treatment on quality of life are unclear. While some population studies have reported no difference in the quality of life between patients with SH and healthy individuals,[11,12] another study determined impairment of quality of life in patients with SH compared to healthy individuals.[13]

Quality of life has become an important concept and objective in research and practice in the fields of health and medicine. Understanding quality of life is important to the amelioration of patients' symptoms and to improving care and rehabilitation. Problems with the self-reported quality of life can lead to changes and improvements in treatment and care, and some treatments may be of very little benefit. In addition, quality of life is also employed to determine the presence and effects of problems capable of affecting patients.[14]

The purpose of this study was to determine the effect of sleep problems on quality of life in patients followed-up due to SH.

Materials and Methods

Approval for the research was granted before commencement by the Kırklareli University ethical committee, Turkey. The confidentiality and anonymity of findings were preserved (According to the Helsinki Declaration). The research was planned as a descriptive, cross-sectional study.

Study design and sampling

The study was performed with patients presenting on an outpatient basis to two separate clinics of the internal diseases of a teaching and research hospital in Turkey between February and July 2021. The population of the study consisted of 92 patients diagnosed with SH who applied to the internal medicine outpatient clinic of a training and research hospital in the previous year (January-December 2020). Accordingly, it was calculated that the study sample should consist of 75 patients with 95% confidence and a 5% margin of error using the formula n=Nt2pq/d2 (N-1)+t2pq. The sample of the study consisted of 103 patients.

Inclusion criteria were no levothyroxine use, voluntary participation, age 18 or over, the ability to communicate and cooperate, and questions being answered fully and completely. fT3, fT4 and TSH values were measured in all patients, and those with normal fT3 and fT4 values and high TSH values were included in the study. Patients who have subclinical hyperthyroidism, using sleeping medications, antidepressants, or anxiolytics, were excluded.

Data Collection Tools

The study data were collected using a questionnaire for participants' descriptive characteristics developed by the authors, the Pittsburg Sleep Quality Index (PSQI), and the Rolls Royce Quality of Life Scale at face-to-face interviews, these being applied once for each patient. This process lasted approximately 15 min.

The form investigating participants' sociodemographic and clinical characteristics consisted of nine questions.

The PSQI was developed by Buysse et al. (1989) and adapted into Turkish by Agargun et al. (1996). This self-report scale evaluates sleep quality and sleep disturbances in the previous month. The scale consists of 24 items, five of which are answered by the individual's partner or roommate (if applicable). The 19 items scored on the scale generate seven components. Each component is evaluated between 0 and 3. The total possible scores of the seven components range between 1 and 21, and a total scale score is calculated. Higher scores indicate greater sleep quality impairment.

The Rolls Royce Quality of Life Scale has been used in numerous disease groups, such as chronic kidney failure, kidney transplantation, cardiological diseases, and cancer. The validity and reliability of the Turkish language version were confirmed by Ozyilan et al. (1995). The scale consists of 42 items and eight sub-dimensions. Higher scores indicate a greater quality of life.

Statistical Analysis

Data analysis was performed on SPSS 21.00 for Windows software. Descriptive statistics are expressed as mean (X) ± standard deviation (SD), number (n), and percentage (%). Correlation analysis was performed using Pearson's correlation test. Effects between scale scores were analyzed using the linear regression test. p values <0.05 were regarded as statistically significant.

Results

The distribution of participants' sociodemographic characteristics is shown in Table 1. Participants' mean age was 44.46±14.12 years, and the mean duration of disease was 7.01±4.90 years. In addition, 75.73% were men, 76.69% were married, 48.54% were elementary school graduates, 65.05% were not in employment, 56.31% had income equal to their outgoings, and 55.32% had no other chronic disease. The most common accompanying disease, with a prevalence of 42%, was hypertension.

Table 1. Participants' Sociodemographic Characteristic Distributions

Characteristic		**X ± SD**	**Min-Max**
Age		44.46±14.12	19-73
Time since diagnosis		7.01±4.90	1-30
		n	**%**
Gender	Female	25	24.27
	Male	78	75.73
Marital status	Married	79	76.69
	Single	24	23.31
Education	Elementary	50	48.54
	High school	28	27.18
	University	25	24.28
Employment status	Working	36	34.95
	Not working	67	65.05
Income	Less than outgoings	45	43.69
	Equal to outgoings	58	56.31
Other chronic diseases	Yes	46	44.68
	No	57	55.32
Chronic diseases*	Hypertension	29	41.98
	Diabetes Mellitus	23	33.28
	Asthma	11	16.02
	Heart diseases	6	8.72

*n was folded

The distribution of participants' mean quality of life and sleep quality scores is shown in Table 2. It was found that participants' total Rolls Royce Quality of Life score mean was 104.99±18.48, and the mean PSQI total score was 7.11±3.75. The mean score of the participants' quality of life was below the moderate level, and sleep quality was at the moderate level.

Table 2. Participants' Mean Sleep Quality and Quality of Life Scale Scores

Scale		**X ± SD**	**Min-Max**
Quality of Life	General Well-Being	19.83±4.59	9-33
	Physical Symptom Activity	24.13±4.66	12-36
	Sleep Disturbances	8.77±2.68	3-15
	Appetite	6.42±1.85	2-10
	Sexual Dysfunction	11.33±3.49	4-20
	Cognitive Functions	18.57±5.46	6-28
	Medical Interactions	11.98±2.79	6-19
	Social Relationships	23.19±4.81	11-37
	Total Score	104.99±18.48	52-159
Sleep Quality	Subjective Sleep Quality	1.37±0.78	0-3
	Sleep Latency	1.49±0.94	0-3
	Duration Of Sleep	0.87±1.09	0-3
	Habitual Sleep Efficiency	0.42±0.78	0-3
	Sleep Disturbances	1.58±0.68	0-3
	Use Of Sleeping Medication	0.27±0.67	0-3
	Daytime Dysfunction	1.09±0.96	0-3
	Total PSQI	7.11±3.75	0-17

Correlations between participants' mean total PSQI and quality of life scores are shown in Table 3. A low negative correlation was observed between mean total PSQI scores and mean physical symptom-activity, sleep disturbance and medical interactions. A moderate negative correlation was found between participants' mean total PSQI scores and mean cognitive function, social relationships scores and total quality of life scores. Mean physical symptom-activity, sleep disturbance, medical interactions, social relationships, cognitive function, and total quality of life scores decreased in line with participants' total PSQI scores.

Linear regression analysis was also performed (Table 4). The model constructed to examine that effect was significant ($p<0.05$). The results showed that impairment of sleep quality adversely impacts the quality of life (beta=-0.316, $p<0.001$). Sleep quality explains 10% of the change in the quality of life.

Table 3. Correlation between Participants' Mean Quality of Life and Sleep Quality Scores*

Scales	Total PSQI	
Quality of Life	**r**	**p**
General Well-Being	0.05	0.59
Physical Symptom Activity	-0.19	**0.047**
Sleep Disturbances	-0.25	**0.009**
Appetite	-0.06	0.52
Sexual Dysfunction	-0.18	0.06
Cognitive Functions	-0.30	**0.002**
Medical Interactions	-0.22	**0.025**
Social Relationships	-0.34	**0.026**
Total Score	-0.33	**0.001**

*Pearson correlation analysis

Table 4. The Effect of Sleep Quality on Quality of Life*

Dependent Variable	Independent Variable	Unstandardized Coefficients		Standardized Coefficients	t	p	R^2
		B	Std. Error	Beta			
Quality of Life	Constant	115.547	3.611		31.995	<0,001	0,10
	Sleep Quality	-1.566	0.450	-0.327	-3.482	0,001	

* Linear regression analysis

Discussion

The findings of this study show that the sleep quality of the patients followed up for SH is at a moderate level, while the quality of life is below the moderate level. Impairment of sleep quality is adversely correlated with quality of life, the latter being adversely affected by impairment in the former. Sleep quality affects 10% of the quality of life.

Linlin et al. reported a significant association between poor sleep and SH in a study from China. Longer sleep latency, shorter duration of sleep, and greater sleep disturbance were observed in the SH group compared to the euthyroid group.[15] In a previous study, Haruko Akatsu et al. reported higher PSQI scores in a group with SH compared to a euthyroid group, together with greater impairment of sleep quality. In addition, impairment of sleep quality increased in line with TSH levels in the euthyroid group.[16] However, Benedetta Demartini et al. reported no significant difference in sleep disturbances between euthyroid individuals and those with SH.[17]

Quality of life is a highly important health objective, one that reflects the ultimate aim of all health interventions. At the same time, it is also measured as physical and social functioning and perceived well-being. Research into clinical and educational interventions emphasizes that patients' quality of life improves as a result of improving their health status and their perceptions of controlling their disease. In methodological terms, it is important to employ multidimensional evaluations of the quality of life and to include both general and disease-specific measures. Quality-of-life measures should be employed to manage and evaluate therapeutic interventions.

Suwalska observed an adverse impact of hyperthyroidism on quality of life. Depressive symptoms were detected in 40% of cases of hyperthyroidism, and a positive correlation was determined between anxiety and quality of life.[18] Martin reported that thyroid hormone use was not associated with improvement in either general quality of life or thyroid-related symptoms in non-pregnant adults with SH and that these findings did not support the routine use of thyroid hormone therapy in adults with SH.[19] In the same way, Parle et al. found no evidence that T4 replacement therapy improved cognitive functions in patients with SH.[20]

The majority of cross-sectional studies have determined mild functional learning impairment and recall problems in young subjects with hypothyroidism.[21] In addition, a community-based study reported an association between Alzheimer's disease and SH.[22] Quijano et al. performed a survey study involving 15 individuals with SH and 15 with clinically mild hypothyroidism. The clinically mild hypothyroidism cases exhibited poorer cognitive status during recording compared to the SH group, while normal cognitive status was determined in both groups after treatment.[21]

Various other studies have observed an improvement in memory performance, frontal executive functions, and some aspects of cognitive performance in individuals diagnosed with SH following levothyroxine therapy.[23]

A prospective community-based study involving participants aged between 85 and 89 showed that initially increasing TSH levels were associated with significant slowing in daily living activities.[24] One study using data from the Korean Study on Health and Aging involving Korean individuals aged over 65 reported an association between cognitive impairment, depression, or poor quality of life in elderly individuals with SH.[25]

The findings of this study show that the total sleep quality score mean of the participants was moderate, and the quality of life decreased in parallel with the deterioration in sleep quality. In terms of the quality of life subdimensions, physical symptoms-activity, medical interactions, social relationships, and cognitive functions, in particular, were affected by sleep quality. Since sleep quality affects the quality of life in patients followed up with subclinical hypothyroidism, sleep assessment is recommended. In addition, it is recommended to take initiatives to increase sleep quality and to investigate different factors affecting the quality of life.

Limitations

The principal limitations of this study are its single-center nature and the fact that it involved only a single diagnosis.

Ethical Considerations: Approval for the research was granted before commencement by the Kırklareli University ethical committee, Turkey (no. E-69456409-199-1835 dated January 2021). Institutional permission was granted by the center where the research was conducted and written, and verbal informed consent was obtained from individuals agreeing to take part. Written permission for the use of the scales employed was also obtained beforehand.

Conflict of Interest: The authors declare no conflict of interest. No funding was obtained for this study.

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PERIPHERAL LYMPHADENOPATHY AND INFECTIONS: EVALUATION OF 197 CASES

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Abstract

Objectives: In our study, we aimed to evaluate the causes of peripheral lymphadenopathy (LAP).

Materials and Methods: Patients older than 18 years old who were diagnosed with LAP and underwent peripheral lymph node biopsies between 01.11.2017 and 01.01.2020 were included in the study. The demographic data and histopathological findings of the patients were retrospectively reviewed on the computer database of the hospital.

Results: One hundred ninety-seven adult patients in total were included in the study, 51.27% (n=101) of whom were female. The rates of fever, night sweats, and weight loss symptoms were detected as 8.63%, 13.70%, and 20.30%, respectively. Excisional biopsy was performed in 93.40% of the patients, and the most frequently excised lymph node was the axillary node at a rate of 40.10%. According to the results of the histopathological analyses, the most common etiology was malignancy, and the second one was infectious, at 31.98% and 29.95%, respectively. Malignancy was caused by lymphoma in 93.65% of the cases, whereas the infectious etiology was caused by tuberculosis at 74.58%. A specific diagnosis could not be made for 26.90% of the cases, and their outpatient follow-up was continued.

Conclusion: Although LAP is often associated with infections, it also occurs as a manifestation of malignant diseases. In our study, the most common etiology was malignant diseases. Infections were the second most common etiology, and among infections, tuberculosis was the leading one. LAP is a frequently encountered clinical condition that is difficult to manage. To avoid delays in diagnosis, patients should be carefully evaluated and followed closely. Although a specific diagnosis cannot always be made, histopathology remains the gold standard for diagnosis.

Keywords: Lymphadenopathy, peripheral, etiology, tuberculosis.

Introduction

Lymphadenopathy (LAP) describes conditions in which lymph nodes are abnormal in size, consistency, or number, and it may be one of the symptoms of various diseases.[1,2] In general, the normal lymph node size is defined as less than 1 cm in diameter, albeit varying based on age and geography.[1-3]

Although peripheral LAP often develops due to self-limiting local or systemic infections, it can be a manifestation of an underlying malignant disease.[1] Autoimmune disease, drugs, and iatrogenic causes also play a role in its etiology.[2,3] Infectious etiologies include viral, bacterial, mycobacterial, fungal, and parasitic agents.[2-4]

Lymphadenopathy is a common clinical condition that causes concern in both patients and physicians.[3] Histopathological diagnosis with biopsy is the gold standard in determining its etiology.[1] The physician should make precise decisions on which patient should be followed observationally and which patient needs a quick workup to prevent possible delays in diagnosis.

We aimed in our study to review the histopathology findings and infectious causes that play a role in etiology in patients who presented with peripheral lymph node enlargement and underwent lymph node biopsy in their follow-ups.

Materials and Methods

Patients older than 18 years old, who presented to the infectious diseases outpatient clinic or were referred from other clinics for consultation between 01.11.2017 and 01.01.2020, and underwent lymph node biopsies after the detection of peripheral LAP, were included in the study. Patients with lymph node enlargement who were being followed up with the diagnosis of conditions such as malignancies or infectious diseases before their inclusion were excluded from the study.

The demographic information of the patients, the durations of their lymphadenopathy, their lymph nodal biopsy sites, the types of their biopsies, laboratory tests, imaging findings, and histopathological findings were retrospectively screened from the hospital's computer database. The obtained information was recorded in the data collection forms that were created by the researchers.

Statistical analysis

Descriptive statistics are expressed as frequency, percentage, and median values.

Results

One hundred ninety-seven adult patients in total were included in the study, 51.27% (n=101) of whom were female. The median age of the patients was 52 years (18-91). Generalized LAP was detected in 88.83% (n=175) of the patients. The time between symptom onset and admission was categorized as three months or shorter, 3-6 months, and six months or longer, and 58.89% (n=116) of the patients had complaints for three months or shorter. The rates of fever, night sweats, and weight loss symptoms among the patients were found as 8.63%, 13.70%, and 20.30%, respectively. Hepatomegaly was found in 24.87% (n=49) of the cases, and splenomegaly was found in 20.81% (n=41). It was found that 93.40% (n=184) of the biopsies were excisional. A history of animal contact was present in 9.14% of the cases (Table 1).

The median size of lymph nodes that was evaluated by ultrasound examination was 31 mm (10 mm-100 mm). Clinically, the most significant lymph node was removed in patients with generalized lymph node enlargement. In general, most biopsies were performed in the axillary region (Figure 1).

The histopathological findings of the lymph node biopsies are given in Table 2. The most common diagnosis was malignancy in 31.98% (n=63) of the patients. Reactive LAP was the second most common diagnosis, which was seen in 27.41% (n=54), followed by necrotizing granulomatous lymphadenitis and granulomatous lymphadenitis, at rates of 21.83% (n= 43) and 17.76% (n=35), respectively.

Table 1. Demographic, clinical and laboratory variables of patients followed up with lymph node biopsy

	n	%		n	%
Sex			**Animal Contact**		
Male	96	48.73	Yes	18	9.14
Female	101	51.27	No	179	90.86
LAP			**Organomegaly**		
Generalized	175	88.83	Hepatomegaly	49	24.87
Localized	22	11.17	Splenomegaly	41	20.81
LAP duration			**Laboratory findings**		
≤3 months	116	58.89	Leukocytosis	35	17.80
3-6 months	48	24.36	ESR>30	109	55.32
≥6 months	33	16.75	AST/ALT >ULN	20	10.15
Symptom			**Biopsy type**		
Fever	17	8.63	Excisional	184	93.40
Night sweats	27	13.70	Tru-cut	13	6.60
Weight loss	40	20.30			

(LAP: Lymphadenopathy, ESR: Erythrocyte Sedimentation Rate, ULN: upper limit of normal)

Table 2. Histopathological findings of lymph node biopsies

Findings	n	%
Lymphoma	59	29.95
Reactive Lymphadenitis	54	27.41
Necrotizing Granulomatous Lymphadenitis	43	21.83
Granulomatous Lymphadenitis	35	17.76
Metastasis	4	2.03
Histiocytic Necrotizing Lymphadenitis	1	0.51
Other	1	0.51

According to the overall evaluation results of the microbiological, radiological, and biochemical test results of the patients, along with their histopathological results, 73.09% (n=144) of the cases were associated with specific diagnoses. While malignancy was the most common diagnosis at a rate of 31.98% (n=63), infections were the second most common at a rate of 29.95% (n=59). Tuberculosis was the leading infectious cause, constituting 74.58% (44/59) of the infectious cases, followed by cat-scratch disease 13.56% (8/59). A specific diagnosis could not be made in 26.90% (n=53) of the cases, and their follow-ups continued (Table 3). One of the patients with the diagnosis of lymphoma and three of the patients with the diagnosis of tuberculosis were coinfected with the human immunodeficiency virus (HIV).

Table 3. Etiological distribution of LAP causes in patients with lymph node biopsy

Etiology	n	%	Percentage in the subgroup (%)
Malignancy	**63**	**31.98**	**100.00**
Lymphoma	59	29.95	93.65
Metastasis	4	2.03	6.35
Infections	**59**	**29.95**	**100.00**
TB	44	22.34	74.58
Cat-scratch Disease	8	4.06	13.56
EBV	3	1.52	5.09
Toxoplasmosis	2	1.01	3.39
CMV	1	0.51	1.69
Syphilis	1	0.51	1.69
Other	**22**	**11.17**	**100.00**
Sarcoidosis	20	10.15	90.90
Castleman Disease	1	0.51	4.55
Kikuchi-Fujimoto Disease	1	0.51	4.55
Non-specific	**53**	**26.90**	**100.00**

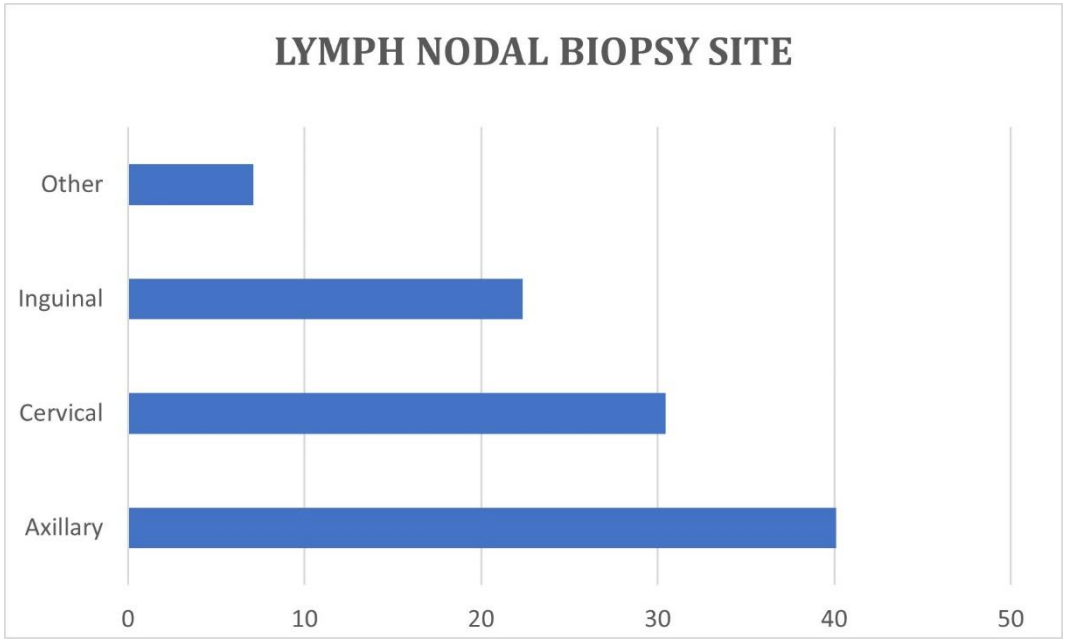

Figure 1. Distribution of lymph nodal biopsy site

Mycobacterium tuberculosis complex grew in the biopsy materials of four patients diagnosed with tuberculosis, bacilli were seen in the Ehrlich-Ziehl-Neelsen staining of the samples of two patients, and three patients had positive polymerase chain reaction (PCR) results for *Mycobacterium tuberculosis*. *Bartonella* indirect hemagglutination (IHA) tests were positive in 50% (n=4/8) of the patients who followed up with the diagnosis of cat-scratch disease. Three patients with EBV-VCA IgM positivity were diagnosed with Infectious mononucleosis, one with CMV IgM positivity was diagnosed with Cytomegalovirus infection, one with VDRL-TPHA positivity was diagnosed with syphilis, and two patients with toxoplasma IgM positivity were diagnosed with toxoplasmosis. Pathological and microbiological findings were evaluated together to determine the etiology in 33.89% (n=20/59) of the patients with LAP associated with infection.

Discussion

Lymph node biopsy is usually performed to investigate possible malignancy. However, some specific histopathological findings suggest infections at diagnosis.[5] In our study, 31.98% of the cases presenting with lymph node enlargement were diagnosed with malignancies, and lymphoma was the leading one among these malignancies. The second most frequent diagnosis was infections, at a rate of 29.95%. Gül et al. reported the rate of malignancies as 34.3%, and Akyüz Özkan et al. reported this rate as 66.5% in their studies examining

the excisional biopsy results of 67 and 185 patients, respectively.[6-7] Similar to our results, lymphoma was found to be the most frequently diagnosed malignant disease in both studies.[6,7] Mabedi et al. also reported malignancy as the most common etiology in patients over the age of 16 in their study, at a rate of 35%. Cetinkaya et al. reported the rate of malignancies as 6.7%, and Yenilmez et al. found this rate as 5% in their multicenter study, including 1401 patients, while the authors found the rates of infection to be 26.6% and 31.3%, respectively.[8-10] In both studies, malignancy rates were found to be lower than those in other studies in the relevant literature, including ours. This may be explained by the fact that patients with suspected malignancy are directed to oncology/hematology outpatient clinics and have fewer admissions to infectious diseases outpatient clinics.[9,10] In our study, patients diagnosed with non-infectious etiologies were directed to the relevant branches for their follow-ups and treatments.

Tuberculosis (TB), caused by the bacterium *Mycobacterium tuberculosis complex*, is one of the oldest known diseases and a significant cause of death worldwide.[11] According to the Turkey Tuberculosis Surveillance 2020 report, in 2018, a total of 11,786 TB patients were diagnosed. While pulmonary involvement is present in more than half of new TB cases, extrapulmonary presentation is mostly seen in the extrathoracic lymph nodes at a rate of 28.8%.[12] For lymphadenitis, the cervical region is the most common site, and cervical lymphadenitis is reported in 60-90% of TB lymphadenitis cases. Tuberculosis remains a problem in both diagnosis and treatment for clinicians, pathologists, and microbiologists.[11] Sunnetcioglu et al. evaluated extrapulmonary TB cases and reported that the disease progressed with lymph node involvement at a rate of 33.4%. In our study, we found *M. tuberculosis* to be the most prevalent among the infectious agents in patients presenting with lymph node enlargement.[13] This result was similar to those reported in previous studies.[6,9,10] In two different studies examining peripheral LAP biopsies in Nigeria and Nepal, TB was also found to be the most common etiology.[14,15]

Tuberculosis and HIV infections constitute the main burden of infectious diseases in countries with limited resources. HIV coinfection is the most significant risk factor for the development of active TB, which can cause both primary infection and TB reactivation in patients with latent TB. *M. tuberculosis* infection also has a negative effect on the immune response against HIV by accelerating the progression from HIV infection to acquired immune deficiency syndrome (AIDS).[16] According to the data of the World Health Organization, the frequency of tuberculosis in individuals living with HIV increases 18 times compared to those not infected with HIV.[17] It is recommended to investigate latent TB in patients diagnosed with HIV and perform prophylaxis when necessary to prevent reactivation.[18] In our study, we detected HIV coinfection in three of our patients diagnosed with TB.

Cat-scratch disease is a self-limited disease typically characterized by lymphadenopathy near a cat scratch or bite site. It is caused by the gram-negative bacterium *Bartonella henselae*. A few days after exposure, a papule

or swelling may develop in the area, followed by regional lymphadenopathy 1-2 weeks later. In most cases, it regresses spontaneously, but lymphadenopathy can persist for several months.[19,20] Cat-scratch disease, which is one of the causes of granulomatous lymphadenitis, should be considered in the differential diagnosis of acute, subacute, or chronic lymphadenopathy.[20] Enzyme immunoassay, indirect immunofluorescence assay, and molecular tests on tissue specimens have been evaluated for diagnosis.[19] We detected cat-scratch disease as the second most common infectious etiology in patients presenting with lymph node enlargement.

Epstein-Barr virus (EBV), the most common infectious disease in adolescents, is among the causes of LAP. The rate of seropositivity in the adult age group is around 90%.[21] The clinical condition is characterized by lymphocytosis, sore throat, lymphadenopathy, and fatigue, which can last for several weeks.[21,22] In our study, EBV, CMV, syphilis, and toxoplasmosis were among the other infectious etiologies.

Although LAP classically defines lymph nodes larger than 1 cm in diameter, supraclavicular, iliac, and popliteal lymph nodes that can be palpated at any size and epitrochlear lymph nodes larger than 0.5 cm in diameter are also considered abnormal.[1,2,23] In many LAP cases developing due to infections, it is often difficult to confirm the presence of microorganisms. In the evaluation of lymph node enlargement cases, first of all, a good anamnesis should be taken, and a physical examination should be performed.[1-3] Associated symptoms may be helpful for diagnosis. Fever, chills, night sweats, weight loss, and localized symptoms may be prodromal symptoms.[2-3] The most common symptom accompanying lymphadenopathy in our patients was weight loss, followed by night sweats and fever, at rates of 20.30%, 13.70% and 8.63%, respectively. Patients should be questioned regarding travel history, infectious agent exposure, animal contact, drug use, and high-risk sexual behaviors.[1-3] Animal contact was present in only 9.14% of our cases.

In cases where patients are evaluated as low-risk in terms of malignancy or serious disease, they can be followed up for 3-4 weeks to monitor whether the enlargement will regress. If the lymph node enlargement does not regress, a biopsy should be performed for diagnosis.[1,3] A specific diagnosis could not be made in 26.90% of our cases. In various studies conducted in Turkey, the rate of patients who could not get a specific diagnosis according to lymph node biopsy results has been reported as 28.4-63.3%.[6,9,10]

In addition to histopathological findings, clinical, serological, and microbiological investigations, especially molecular examinations, form the basis of diagnosis.[5] Molecular methods are recommended as the gold standard in the diagnosis of infectious lymphadenitis; culture remains critical in diagnosis, particularly for fastidious bacteria and mycobacteria. Clinicians should keep in mind that infection cannot be excluded even if molecular tests are negative.[24] Pathological and microbiological examinations were evaluated together in the diagnoses of 33.89% of our patients who were followed up for infection.

The major limitation of our study was its retrospective design. There are few studies on this subject, and they have been carried out mostly with the pediatric patient population. Although more comprehensive and prospective studies are required, we think that our study, in which we evaluated the etiology of LAP in terms of infectious diseases, will contribute to the literature.

In conclusion, we found tuberculosis in the first place among infectious etiologies. Tuberculosis continues to be a significant public health issue worldwide. As people living with HIV should be screened for TB, patients diagnosed with TB should also be screened for HIV infection. Although the cat-scratch disease cannot always be proven by serological tests, animal contact should be questioned and considered in the differential diagnosis of LAP. Even though infectious mononucleosis is frequently seen in pre-adolescent age groups, it should be kept in mind that it can be seen in any age group. LAP is a frequently encountered clinical condition that is difficult to manage. A specific diagnosis cannot always be made, but the gold standard for diagnosis is still histopathology. Close follow-up of patients with non-specific diagnoses should be continued.

Ethical Considerations: The study was approved by the Institutional Ethics Committee of the İstanbul Medeniyet University, Göztepe Training and Research Hospital (30.06.2021, 2021/0352).

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

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Research Article

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SJÖGREN'S SYNDROME: IS IT JUST DRYNESS?

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Abstract

Objectives: Sjögren's syndrome (SS) is the most common autoimmune, multisystemic rheumatic disease. The wide spectrum of the signs and symptoms of SS often causes difficulties in diagnosis. Patients can apply with different complaints to general practitioners and many different specialists, apart from internists and ophthalmologists, who frequently encounter the disease. Our aim in this study was to evaluate the initial complaints of the patients who have been diagnosed with SS.

Materials and Methods: Sixty-six patients who were diagnosed with primary SS according to 2012 or 2016 classification criteria were included in the study. The clinical and laboratory features were retrospectively evaluated.

Results: The female/male ratio was 60/6. The initial complaint of most patients (n:34) was arthralgia or arthritis (51.51%). ANA was positive in 56 patients (84.84%), RF in 19 (28.78%), but not evaluated in 7 (10.6%), anti-SS-A in 29 (43.93%), and anti-SS-B in 16 (24.24%). Sixty-three patients had a positive Schirmer test. Minor salivary gland biopsy was obtained in 42 patients, and 28 had biopsy findings consistent with SS.

Conclusion: SS is a common disease with a wide variety of clinical presentations. A detailed evaluation of patients is necessary to provide an accurate diagnosis and proper care.

Keywords: Sjögren's syndrome, sicca symptoms, anti-nuclear antibody, Schirmer test.

Introduction

Sjögren's syndrome (SS) is an autoimmune, multisystemic rheumatic disease characterized by sicca symptoms in the eye and mouth caused by the inflammation in salivary and lacrimal glands.[1,2] SS may occur alone. In that case, it is called primary Sjögren's syndrome (pSS) or may be linked to another autoimmune disease and called secondary Sjögren's syndrome (sSS).[3]

PSS is considered to be the most common disorder among all chronic systemic rheumatic diseases.[4] It is more common in females, with a gender ratio of 9:1.[5] Clinical features of SS may be due to exocrine involvement or extra-glandular manifestations.[6] Diagnosing sSS may be easier because of the already diagnosed primary disease. But the wide spectrum of the signs and symptoms of SS often causes difficulties in diagnosis, especially in pSS.[7] Sicca symptoms are common in the general population. Other serious symptoms such as chronic pain, major organ involvement, neuropathies, and lymphomas are so heterogeneous, which makes early diagnosis difficult.[7] Patients can apply with different complaints to general practitioners and many different specialists, apart from internists and ophthalmologists, who frequently encounter the disease, resulting in a delay in diagnosis. Early diagnosis and referral to a rheumatologist are important for preventing serious complications. There are studies ongoing to deeper the characteristics of the disease or find novel biomarkers that may allow an earlier diagnosis.[6] Herein, we aimed to evaluate the initial complaints of the patients who have been diagnosed with SS in a tertiary center internal medicine outpatient clinic.

Materials and Methods

Sixty-six patients who were diagnosed with pSS, according to 2012 or 2016 classification criteria, in our hospital's Internal Medicine Department between 2019-2022 were included in the study.[8,9] The clinical and laboratory features, including the autoantibodies anti-nuclear antibodies (ANA), anti-SS-A, anti-SS-B, and rheumatoid factor (RF), Schirmer test results, and salivary gland biopsy findings, were retrospectively evaluated.

The study was approved by the Eskisehir Osmangazi University Ethics Committee. The study was carried out in accordance with the statement of the Helsinki Declaration. Informed consent was obtained from each participant.

Statistical Analysis

Continuous data are presented as mean ± standard deviation. Categorical data are presented as a percentage (%). IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) is used for analysis.

Results

A total number of 66 patients who were diagnosed with pSS were included in the study. The mean age of the patients was 52.92±12.73 (20-82), and the majority of the patients were female (60/66). The initial complaint of most patients (n:34) was arthralgia or arthritis (51.51%), followed by widespread pain in 9 (13.64%), dry eyes in 6 (9.10%), pulmonary symptoms in 5 (7.58%), hematologic disorders in 3 (4.54%), dry mouth in 3 (4.54%), the positivity of serologic tests in 2 (3.03%) and other non-specific complaints in 4 of them (6.06%). The initial complaints of the patients are shown in Table 1. Of the 66 patients, 44 (66.67%) had fatigue, 46 (69.70%) had complaints of dry eye, and 43 (65.15%) had dry mouth when questioned (Table 2).

Table 1. Initial complaints of the patients

Initial complaint	**Number of patients (n=66)**
Arthralgia/arthritis	34 (51.51%)
Widespread pain	9 (13.64%)
Dry eyes	6 (9.1%)
Pulmonary symptoms	5 (7.58%)
Hematologic disorders	3 (4.54%)
Dry mouth	3 (4.54%)
Serologic test positivity	2 (3.03%)
Other	4 (6.06%)

Table 2. The symptoms of the patients in the questioning in terms of Sjögren's syndrome and physical examination findings

Symptom/ physical examination finding	Number of patients (n=66)
Fatigue	44 (66.67%)
Dry eye	46 (69.69%)
Dry mouth	43 (65.15%)
Arthritis	4 (6.06%)
Fibromyalgia	19 (28.78%)

On the physical examination, four patients (6.06%) had arthritis, and 19 (28.78%) patients' fibromyalgia points were tender. The mean erythrocyte sedimentation rate (ESR) was 30.43±18.21 (5-81), and the mean C-reactive protein (CRP) level was 5.53±6.19 (0-26.2).

ANA was positive in 56 patients (84.84%), RF in 19 (28.78%), but not evaluated in 7 (10.6%), anti-SS-A in 29 (43.93%), and anti-SS-B in 16 (24.24%). The majority of the ANA-positive patients had low titers (66.07% had +1 and +2 positivity), and the most common staining pattern of ANA was granular (65.15%). Details of ANA test results are summarized in Table 3.

Schirmer test was available in our hospital, and 63 patients had positive test results. Minor salivary gland biopsy was obtained in 42 patients, and 28 had biopsy findings consistent with SS.

Table 3. ANA staining patterns of the patients

ANA staining patterns	**Number of patients (50)***
Granular [n (%)]	43 (65.15%)
Nucleolar [n (%)]	20 (30.3%)
Homogenous [n (%)]	7 (10.6%)
Centromere [n (%)]	1 (1.51%)

*Some patients had two different types of staining

Discussion

SS is known as the most common systemic rheumatic disease, and patients mostly apply to clinics other than rheumatology. A careful medical history and physical examination may facilitate diagnosis. This study aimed to define the initial complaints and clinical findings of SS patients.

SS has an unbalanced gender ratio close to a 10/1 female/male ratio was reported in a big data study of >14,000 patients with SS.[10] Exactly similar to the existing data, the female/male ratio in our study was 10/1. SS can occur at all ages but is mainly diagnosed between 30 and 50 years of age.[11] Even though the mean age of the patients in our study group was a little older (52.92±12.73 yrs), there was a wide range (20-82 yrs). Diagnosing SS sometimes may be a challenge; mild symptoms may cause a delay in diagnosis, which may be the explanation for the particular old age of our study population.

Even SS is characterized by dry eyes and mouth, arthralgia-arthritis, and widespread pain were the initial complaints of most patients. Similar to our results, arthralgia and polyarthritis were the most common extra-glandular manifestations of SS in a study from Spain.[12] On the other hand, dry eyes and mouth were less common complaints. Patients are more mindful of pain rather than dryness symptoms or may fail to identify

dryness, especially ocular dryness. Clinicians must always keep in mind SS when evaluating a patient with pain. It may be useful to ask questions such as "Have you had daily, persistent, troublesome dry eyes for more than three months?", "Do you have a recurrent sensation of sand or gravel in the eyes?", or "Do you use tear substitutes more than three times a day?" when questioning dry eye.[13] Increased acute phase reactants may be a clue to autoantibodies.

One of the reasons for diagnostic difficulties, patients may not be aware of ocular dryness. It was the initial symptom of 6 patients (9.10%), but 46 patients (66.70%) complained when questioned, and 95.45% had positive Schirmer test results in our cohort. So, dry eye may not be ruled out without performing objective tests. In our hospital, the Schirmer test was available by the time period of the study, but break-up time and topical application of vital stains (lissamine green or fluorescein) may also be used.[14]

Autoantibodies help diagnose SS, ANA, anti-SS-A, and anti-SS-B are used in the latest classification criteria for SS.[8] RF was used in the former criteria.[9] Among these, ANA has the highest positivity rate, followed by anti-SS-A, anti-SS-B, and RF, in decreasing order.[14] The frequency of ANA, anti-SS-A, anti-SS-B, and RF positivity were in line with the literature in our cohort (84.84%, 43.93%, 24.24 %, and 28.78%, respectively).[14]

Minor salivary gland positivity (showing focal lymphocytic sialadenitis with a focus score ≥1) was shown in 66% and 89% of patients with pSS in different studies.[15,16] Our patient population's positivity rate was 66.67%, similar to the literature.

Our study has some limitations. The most important one is the retrospective evaluation of the patients, which may have caused a loss in data. Also, the small number of the patients included in the study may avoid generalization, but the study was conducted during the Coronavirus disease 2019 (Covid-19) pandemic, and a limited number of patients applied to the hospital. An objective test for salivation was not used. Finally, a minor salivary gland biopsy was not obtained for all participants due to Covid-19 restrictions.

In conclusion, SS is a common disease with a wide variety of clinical presentations. A detailed evaluation of patients is necessary to provide an accurate diagnosis and proper care. Sicca symptoms may not always be dominant, so careful evaluation needs for an exact diagnosis. Also, collaboration between clinics helps to facilitate early and correct diagnosis.

Ethical Considerations: The study was approved by the Eskisehir Osmangazi University Ethics Committee (Approval No: 43, dated Feb 15, 2022). The study was carried out in accordance with the statement of the Helsinki Declaration. Informed consent was obtained from each participant.

Conflict of Interest: The authors declare no conflict of interest. No funding was obtained for this study.

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Research Article

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CAN WE USE THE TRIGLYCERIDE/HDL RATIO TO DETERMINE INSULIN RESISTANCE IN OBESITY SCREENING AND FOLLOW-UP IN PRIMARY CARE?

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Abstract

Objectives: Obese patients are followed up with periodic laboratory tests. Insulin resistance is also a parameter used in these tests. There is a need for parameters that can determine insulin resistance more easily and practically. The aim of our study is to investigate the discriminative power of triglyceride (Tg) and triglyceride/high-density lipoprotein cholesterol ratio (Tg/HDL) for Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) in our patient population by examining the laboratory findings.

Materials and Methods: In this retrospective study, the laboratory data of patients who applied to the Family Medicine Obesity Polyclinic of Düzce University Hospital between April 2018 and April 2019 with the desire to lose weight and/or have healthy lifestyle suggestions were examined.

Results: Of the 512 patients included in our study, 66.40% (n=340) were female and 33.59% (n=172) were male. In the examination performed on patients grouped according to their Body Mass Index (BMI), Total cholesterol, HDL, Low-density lipoprotein (LDL), Tg, HOMA-IR, Insulin and Tg/HDL ratios were significantly different between the groups. The cut-off value in the ROC analysis of the Tg/HDL parameter between patients with and without insulin resistance was found to be 2.29 with 66% sensitivity and 55% specificity (AUC: 0.634, $p<0.001$). In Spearman's correlation analysis of Tg/HDL and HOMA-IR, both parameters were found to have a statistically significant correlation (r: 0.248; $p< 0.000$).

Conclusion: The significant relationship between the high Tg/HDL ratio and HOMA-IR detected in the results of our study shows that the Tg/HDL ratio can be used as a practical tool to evaluate insulin resistance in obese patients.

Keywords: Obesity, insulin resistance, HOMA-IR, Tg/HDL.

Introduction

As it is known, obesity is a disease that is common in our age and has high mortality and morbidity.[1] In the clinic, patients are evaluated by body mass index (BMI), which is expressed as body weight in kilograms divided by square meter height for obesity screening and diagnosis. According to some cut-off values patients are classified as; underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), obese grade I (30.0-34.9 kg/m^2), obese grade II (35.0-39.9 kg/m^2) and obese grade III (40.0+ kg/m^2).[2] In addition to BMI and various anthropometric measurements, patients are followed up with periodic laboratory tests. HOMA-IR is also a parameter used in these examinations.[3] Detection of insulin resistance can also identify individuals at high risk for diseases such as cardiovascular and diabetes.[4] In order to measure insulin resistance, it is necessary to determine fasting insulin. However, fasting insulin is not a primary care examination, and it is a costly method in a hospital setting.[5] Some studies have formed the idea that insulin resistance in patients can be detected by using the ratio between Tg and HDL, which can also be done in primary care.[6,7] However, this ratio is not yet in routine use due to some conflicting results.[8] It is interpreted that these conflicting results may be related to the variability of the study population.[9] According to our literature search, we found that the Tg/HDL ratio of patients classified according to the BMI index was not studied in a large patient population in our country. The aim of our study is to investigate the discriminative power of the Tg/HDL ratio for HOMA-IR in our patient population by examining the examinations of patients who applied to the healthy living and obesity outpatient clinic in our university hospital.

Materials and Methods

In this retrospective study, the laboratory data of patients who applied to the Family Medicine Obesity Polyclinic of our University hospital with the desire to lose weight and/or healthy lifestyle suggestions between the dates of the year 2018-2019 were examined. Ethical permission for the study was obtained from the local ethics committee.

Study Group

During the study period, 1823 patients were admitted to the obesity outpatient clinic. Chronic diseases such as heart and kidney diseases, thyroid diseases, liver diseases, serious infections, malignancy or taking any drug known to cause discomfort in lipid metabolism were excluded from the study. Since the BMI and laboratory tests measured at the time of the first application of the patients were used for the study, recurrent applications were also excluded from the study. Finally, a total of 512 patients were included in the study (Figure 1).

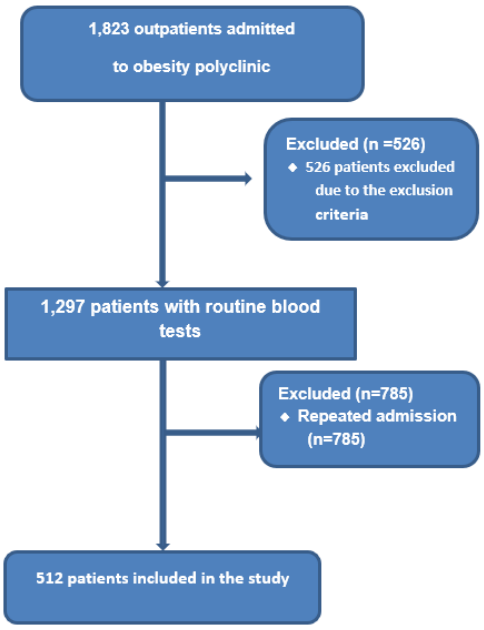

Figure 1. Study design and process

Blood samples were taken after at least 8 hours of fasting. All measurements were carried out in Düzce University Research and Application Hospital Biochemistry Laboratory. From blood tests, fasting blood glucose (FBS), insulin, total cholesterol, LDL, HDL, and Tg levels were scanned. Insulin resistance was calculated with the HOMA-IR formula (fasting glucose (mg/dl) x fasting insulin (μIU/mL) / 405).

Statistical analysis

In descriptive statistics, quantitative data were given as mean and standard deviation, and categorical data were given as numbers and percentages. The distribution of numerical data was examined by using histogram graphics. One-way ANOVA was used for parametric data, and Kruskal Wallis tests were used for non-parametric data to compare data between groups. The cut-off value was calculated in the ROC analysis of the Tg/HDL parameter between patients with and without insulin resistance. The AUC and cut-off value (cut-off value) of each measurement were determined, and the sensitivity, specificity, and LR + cut-off values of these values were calculated and evaluated together. A value of $p < 0.05$ was accepted as statistically significant. Spearman's correlation analysis was used for the relationship between Tg/HDL and HOMA-IR. All statistics were performed by using SPSS 23.0 package program (SPSS, version 23X, IBM, Armonk, New York 10504, NY, USA).

Results

Of the 512 patients included in our study, 66.40% (n=340) were female and 33.59% (n=172) were male. According to the examination made from the routine examinations of the patients grouped according to their BMI, FBS, total cholesterol, HDL, LDL, Tg, HOMA-IR, Insulin and Tg/HDL ratio showed significant differences between groups (Table 1).

Table 1. Comparison of laboratory results of patients and BMI group

Parameters	Group I* (n=126)	Group II* (n=158)	Group III* (n=141)	Group IV* (n= 87)	*P***
Gender (Female/Male)	86/40	93/65	81/60	80/7	**<0.001**
Age	38.21±11.42	40.93±9.63	43.82±9.55	43.92±11.23	**<0.001**
Weight	75.23±11.21	86.32±10.32	98.34±12.34	112.24±15.31	**<0.001**
BMI	27.91±1.61	32.53±1.42	36.93±1.46	44.23±4.23	**<0.001**
FBS	95.82±11.14	95.93±10.60	99.21±13.24	102.13±17.21	**<0.001**
Total Cholesterol	183.10±41.52	199.12±40.94	202.24±41.13	199.91±43.32	**<0.001**
HDL	56.23±17.8	50.49±12.3	49.24±11	47.97±10	**<0.001**
LDL	101.34±32.2	123.68±43.7	118.39±32	123.84±34	**<0.001**
Tg	89 (20-412)	118 (25-565)	127 (38-722)	129 (62-387)	**0.005**
HOMA-IR	2.59±1.21	2.77±1.76	3.81±1.12	4.13±1.73	**<0.001**
Insulin	9.87(1.9-31)	10.29(2.7-61)	12.62 (3.3-79)	12.31 (5.4-59)	**<0.001**
Tg/HDL	1.61(0.3-11.9)	2.46 (0.25-18)	2.82 (0.56-18.8)	2.87 (0.9-10)	**<0.001**

*The patients were grouped according to their BMI
F/M; Female/Male
BMI: Body Mass Index
FBS: Fasting blood sugar
HDL: High-density lipoprotein, LDL: Low-density lipoprotein Tg: Triglyceride
HOMA-IR: Homeostatic Model Assessment of Insulin Resistance
** One-way ANOVA and Kruskal Wallis tests were used to compare data between groups

In the ROC (Receiver Operating Characteristic) analysis of the Tg/HDL parameter between patients with and without insulin resistance; The cut-off value was 2.29 with a sensitivity of 66% and a specificity of 55% (AUC: 0.634, p< 0.001) (Figure 2, Table 2).

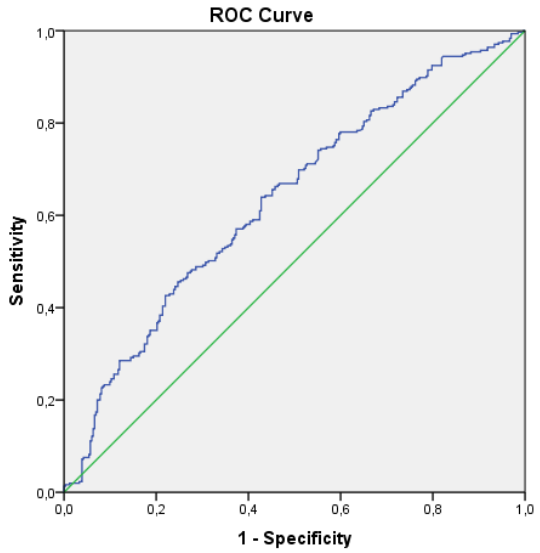

Figure 2. ROC curve of Tg/HDL variables for insulin resistance

Table 2. The cut-off value of Tg/HDL with sensitivity and specificity for insulin resistance

Parameter	AUC (CI)	p	Sensitivity (%)	Specificity (%)	Cut-Off
Tg/HDL	0.634(0.591-0.677)	<0.001	66	55	2.29

AUC: *Area Under the Curve, CI: Confidence Interval*

In Spearman's correlation analysis of Tg/HDL and HOMA-IR, both parameters were found to have a statistically significant correlation (r: 0.248; p<0.001) (Figure 3).

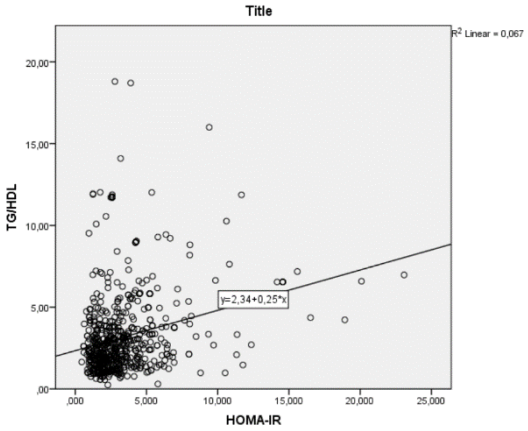

Figure 3. Spearman's correlation plot of Tg/HDL and HOMA-IR

Discussion

In our study, the laboratory findings of patients who applied to our obesity outpatient clinic at the time of their first admission were examined. In order to predict insulin resistance in primary care, it was investigated whether the Tg/HDL ratio is a practical alternative to HOMA-IR. According to our study results, as the obesity degree of the patients increased, it was determined that the FBG and Tg levels increased. Studies have revealed that as BMI increases, impaired glucose metabolism and lipid metabolism are also observed more.[10,11] Effects of insulin on lipid metabolism; insulin suppresses lipolysis in adipose tissue by inhibiting hormone-sensitive lipase, thereby controlling the release of free fatty acids into circulation. Free fatty acids reduce insulin receptor signaling. Fat cells that are saturated with free fatty acids form the infrastructure of insulin resistance with a reverse effect.[12] This dyslipidemia caused by obesity causes permanent changes in the adipose tissue and becomes a vicious circle as a condition characterized by insulin resistance and hyperinsulinemia.[13]

In many studies, the diagnosis of health problems secondary to obesity and the possibility of early treatment in obese patients with simple hematological and biochemical tests have been suggested.[14,15] The most important result of our study is the demonstration of a significant relationship between Tg/HDL and HOMA-IR parameters. Together with the results of ROC analysis of the Tg/HDL parameter among patients with and without insulin resistance, we can say that patients with Tg/HDL ratio above 2.29 have insulin resistance. In a large-scale study in Japan, they found that as the HOMA-IR ratio increased, the Tg/HDL ratio increased. It was also found that Tg/HDL values were lower in both men and women who exercised regularly and had high physical activity.[16] Tg/HDL ratio is considered a useful and practical laboratory parameter in many studies as a predictive marker for HOMA-IR.[17-19] Comparing the usefulness of HOMA-IR markers in the prediction of metabolic syndrome, the TG/HDL-C ratio seems to be the best and is also recommended for use in clinical practice to detect metabolic syndrome.[20] In studies conducted to predict insulin resistance using the Tg/HDL ratio, the cut-off value of this ratio varies between 1.1 and 3.[6,21] In the literature, there is no standard value yet determined for these various rates. However, high Tg and low HDL levels in obese patients, and therefore high Tg/HDL ratios, may provide insight into insulin resistance.

As it is known, preventive health services are the most important component of primary care medicine. Obesity and the diseases it causes are preventable and manageable diseases in primary care. Preventing chronic diseases such as insulin resistance and metabolic syndrome before they occur provides significant advantages to the patient and the health system. Periodic follow-up of physical examination and other routine controls is recommended in obese patients.[22-24] Being able to do these checks and scans in an easy and inexpensive way is very attractive for the primary care physician. Tg and HDL values are a test that can be

evaluated in primary care. In addition, they are tests that can be evaluated practically without sending the patient to the hospital, without any additional cost.

Limitations

Our study has some limitations. First of all, our results cannot be generalized to the whole population since our study was a single-centered study. Since it is a retrospective study, up-to-date information on the patients could not be reached. Longitudinal and large-scale studies are needed in terms of causal relationships.

Conclusion

The significant relationship between the high Tg/HDL ratio and HOMA-IR detected in the results of our study shows that the Tg/HDL ratio can be used as a practical tool to evaluate insulin resistance in obese patients. Practical and inexpensive laboratory parameters that can predict insulin resistance in primary care provide benefits to the patient in preventive health services.

Ethical considerations: Ethical approval for the study was obtained from the ethics committee of Düzce University (Approval No: 2021/228, Date: 01.10.2021).

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

(The results of this study were presented as an oral presentation at the 20th National Family Medicine Congress.)

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Erratum

Subject: Article titled “Role of Atopy in Primary Enuresis Nocturna”

We would like to thank Dear Prof. Dr. İlknur Bostancı for her contributions during the dissertation phase to the article titled "Role of Atopy in Primary Enuresis Nocturna/Primer Enürezis Nokturnada Atopinin Yeri", produced from the thesis and published in Turkish in the Ankara Medical Journal (2014, Volume 14, Issue 1, Page 19-25). We do apologize to her for not writing her name inadvertently because of the mistake made in the article in question.

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