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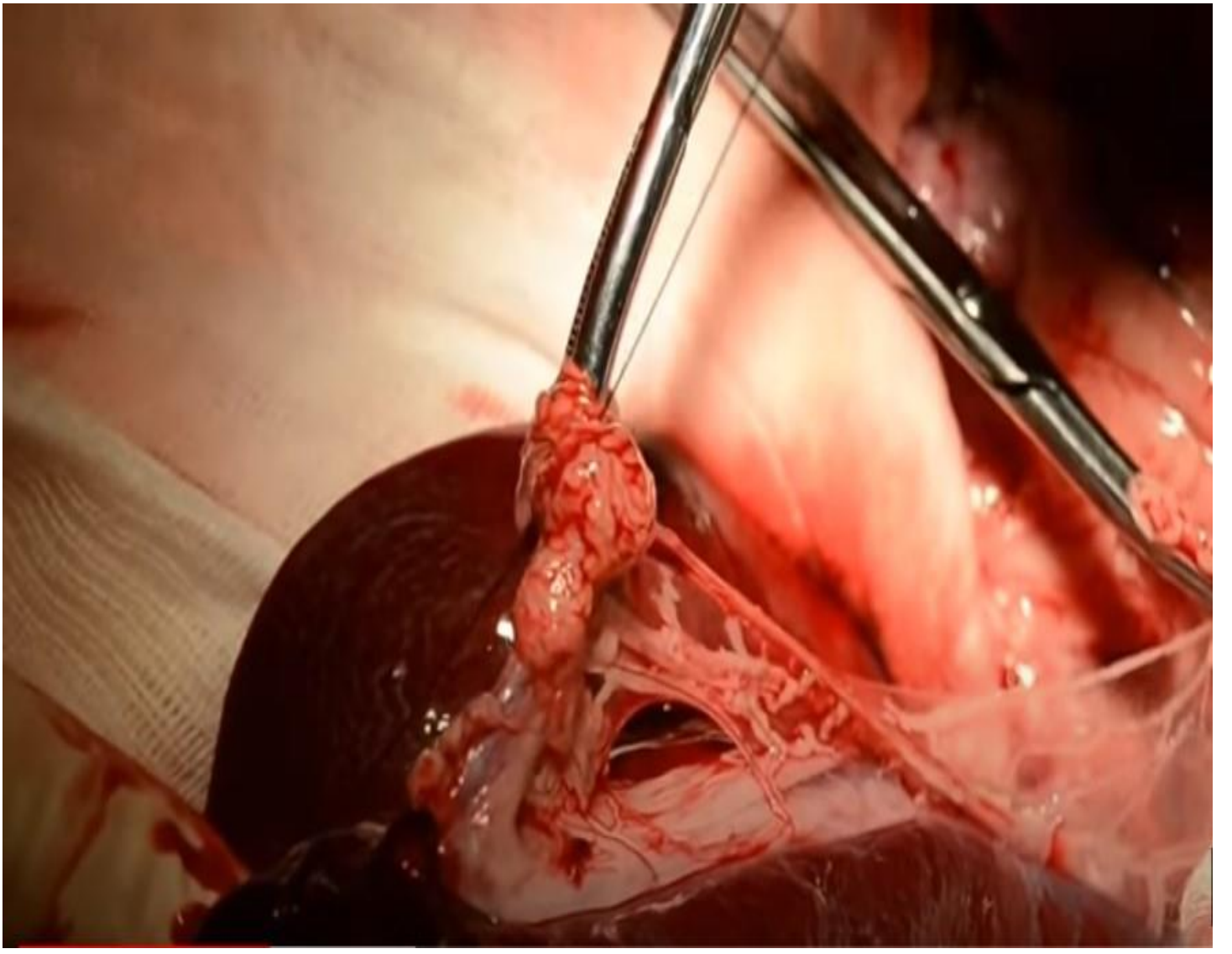

The Role of The Spleen in Atherosclerosis

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Contents

Research Article

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The Role of The Spleen in Atherosclerosis

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ABSTRACT

Objective: Atherosclerosis is a chronic inflammatory process characterized by the accumulation of lipid and inflammatory cells in the walls of medium and large arteries. Metabolic effects of splenectomy are less known, especially the effects on lipid metabolism is a debate. In this study, we aimed to investigate the effects of splenectomy on atherosclerosis in humans.

Methods: The data of 280 patients who underwent a splenectomy at a tertiary center between 2009-2016 were analyzed. The 50 patients were included in the study as a splenectomy group. In addition, 50 patients who applied to our outpatient clinic between January 2021 and August 2021 with similar characteristics to those in the splenectomy group except for splenectomy were included in the study as a non-splenectomy group. Atherosclerosis was evaluated by measuring the right, left, and the mean carotid artery intima-media thickness (CAIMT).

Results: All measurements were significantly higher in the splenectomy group (p=0.010 for left CAIMT, p=0.011 for right CAIMT and p=0.008 for mean CAIMT).

Conclusion: The CAIMT measurements were higher and therefore atherosclerosis risk was increased in patients with splenectomy. For this reason, it should be kept in mind that these patients may develop cardiovascular and cerebrovascular problems due to atherosclerosis and should be followed up in this respect.

Keywords: lipoprotein; carotid artery; vessel; lipid

Research Article

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INTRODUCTION

Atherosclerosis is a chronic inflammatory process characterized by the accumulation of lipid and inflammatory cells in the walls of medium and large arteries (1). It is the main cause of myocardial and cerebral infarctions and related deaths (2). Plasma cholesterol and low-density lipoprotein (LDL) levels are associated with atherosclerosis (3).

The spleen has many functions and effects on different systems. As the functions of the spleen are better understood, the indications for splenectomy have decreased, and spleen-sparing surgeries have become more common. However, splenectomy is still one of the most frequently performed surgeries for such reasons as trauma, hematological diseases, and malignancies.

Hematological and immunological side effects of splenectomy are well-known, besides there are also lesser known metabolic effects. Especially the effects of splenectomy on lipid metabolism is a debate, in addition, there is no human study about atherosclerosis after splenectomy in literature. In this study, for the first time, we aimed to investigate the effects of splenectomy on atherosclerosis in humans.

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MATERIAL and METHODs

The study is a cross-sectional cohort study and the data were obtained from a retrospective database. The data of 280 patients who underwent a splenectomy at a tertiary center between 2009-2016 were analyzed. The inclusion criteria were the age between 20-50 years, having a body mass index (BMI) between 19-30 kg/m^2, being a non-smoker, not using drugs that would affect the lipid profile, having splenectomy for benign reasons, and having passed five years after splenectomy. Finally, 50 patients were included in the study as a splenectomy group. In addition, 50 patients who applied to our outpatient clinic between January 2021 and August 2021 with similar characteristics to those in the splenectomy group except for splenectomy were included in the study as a non-splenectomy group.

Atherosclerosis was evaluated by measuring the right, left, and the mean carotid artery intima-media thickness (CAIMT). The mean CAIMT was determined by dividing the sum of the right and left CAIMT by two. The CAIMT was measured at the carotid artery bifurcation level using Vivid E95 ultrasound system (GE Healthcare, Oslo, Norway) and 11-LD Linear Array Transducer (4.5-12 MHz). Ethical approval was obtained from the institutional Ethical Committee (2906-2021).

Statistical Analysis: The Shapiro-Wilk test was used to assess the normality of the distribution of numerical variables. Numerical variables were given as median (minimum-maximum). Categorical variables were defined as frequency (percentage).

The Mann-Whitney U test was used in between-group comparisons for numerical variables. Categorical variables were analyzed with the Chi-Square or the Fisher's Exact tests. A p value<0.05 was considered significant. The IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA) was used for statistical analyses.

RESULTs

Demographics and medical features of patients are summarized in Table 1. The median age of whole study group was 38 years (20-50). The splenectomy group had higher median age (41 vs 38) but the difference was not significant. Almost half percent of the patients in both groups and in the whole study group were male. The BMI values were similar between the groups. Only three patients had comorbidities and all were in the splenectomy group (one patient with asthma, one patient with multiple sclerosis and one patient with von Willebrand disease). In addition there was only one patient using medication (the patient with asthma used bronchodilator).

Table 2 shows the indications for splenectomy. The most common indication was trauma (n=25, 50%) followed by immune thrombocytopenic purpura and iatrogenic splenic injury. Comparisons and results of CAIMT are given in Table 3. All measurements were significantly higher in the splenectomy group (p=0.010 for left CAIMT, p=0.011 for right CAIMT and p=0.008 for mean CAIMT).

Table 1. Demographics and medical features of patients

	Whole study group (n=100)	Splenectomy group (n=50)	Non-splenectomy group (n=50)	P value
Age (year)	38 (21-50)	41 (21-50)	38 (21-50)	0,249
Gender (male)	51 (51%)	25 (50%)	26 (52%)	0,841
BMI (kg/m^2)	24,30 (19,10-29,60)	24,45 (19,10-29,60)	24,00 (19,00-28,00)	0,233
Comorbidity (yes)	3 (3%)	3 (6%)	-	0,242
Drug use (yes)	1 (1%)	1 (2%)	-	1

BMI: Body mass index

Table 2. Indications for splenectomy of the splenectomy group

	Splenectomy group (n=50)
Trauma	25 (%50)
ITP	13 (26%)
Iatrogenic	4 (8%)
Pancreatic cyst	3 (6%)
Splenic cyst	2 (%4)
Hereditary spherocytosis	1 (2%)
Splenic abscess	1 (2%)
Hemangioma	1 (2%)

ITP: Immune thrombocytopenic purpura

Table 3. Comparisons and results of CAIMT

	Whole study group (n=100)	Splenectomy group (n=50)	Non-splenectomy group (n=50)	P value
Left CAIMT (mm)	0,07 (0,03-0,37)	0,08 (0,04-0,37)	0,06 (0,03-0,37)	**0,010**
Right CAIMT (mm)	0,07 (0,03-0,22)	0,08 (0,04-0,22)	0,06 (0,03-0,16)	**0,011**
Mean CAIMT (mm)	0,07 (0,03-0,24)	0,08 (0,04-0,24)	0,06 (0,03-0,24)	**0,008**

CAIMT: Carotid artery intima–media thickness, Bold values denote statistical significance at the p < 0.05 level

DISCUSSION

The role of the spleen and the side effects of splenectomy on different systems are well known, but their effects are not clear on the development of atherosclerosis. To the best of our knowledge, this is the first study in the literature to investigate the effect of splenectomy on atherosclerosis in humans. In this study, atherosclerosis was evaluated using CAIMT and was found to be significantly higher in patients with splenectomy.

The main pathological process in atherosclerosis is the accumulation of LDL in the subendothelial space. Subendothelial LDL is oxidized by reactive oxygen species, and oxidized LDL (ox-LDL) occurred (4). Hypertension, diabetes mellitus, smoking, and dyslipidemia increase ox-LDL by activating the NADPH-oxidase system (5). Ox-LDL induces the development of atherosclerosis by causing inflammation in the arterial wall (6). B cell-mediated and T cell-mediated inflammation, which is effective in the occurrence of atherosclerosis, is mostly activated by plasma LDL (7). For these reasons, the main strategy in the treatment of atherosclerosis is to reduce blood LDL levels and reduce inflammatory responses.

The spleen is a component of the reticuloendothelial system. Splenectomy has hematological, immunological, and metabolic side effects, but the metabolic ones have not yet been fully elucidated. Many possible mechanisms have been described that explain the effects of the spleen on lipid metabolism. The most popular of these is to be a reservoir for lipids (8). Another theory argues that the spleen produces anti-ox-LDL antibodies via B-lymphocytes (9). In addition, the spleen has a role in LDL metabolism too (10,11). Consequently, different studies presented different results about the effects of spleen and splenectomy on lipid metabolism and atherosclerosis. Some of them found changes in blood lipid levels (12–16) and some of them did not (9,17–21). But almost all of which were experimental. Similarly, some of them found increased atherosclerosis incidence (9,18,19) and some of them did not (20,21). Conversely, a study by Li and Stone stated a lower atherosclerosis incidence (17). Robinette and Fraumeni Jr. found a higher mortality rate due to cardiovascular diseases in veterans with splenectomy, and they argued that this may due to the effect of splenectomy on lipid metabolism (10). In another study, although cardiovascular diseases were found to be higher in veterans with splenectomy, this difference was not observed when those with autoimmune diseases were excluded from the study (22).

In this study, CAIMT measurement via ultrasound was used to evaluate atherosclerosis. It is a cheap, non-invasive, and easily accessible method to evaluate atherosclerosis. While intimal thickening in the carotid artery is associated with atherosclerosis, the thickening of the medial layer is usually related to hypertension-related smooth muscle hypertrophy (23). CAIMT is accepted as a marker for early-stage atherosclerosis (24). In a meta-analysis, it was reported that cardiovascular events may be reduced by reducing the occurrence and progression of CAIMT (24).

While the risk factors for atherosclerosis (such as age, BMI, drug usage, comorbidities, smoking status) were similar between the groups, we found higher CAIMT measurements in the splenectomy group. This indicates splenectomy increases the risk of atherosclerosis. We think that this may be due to the effects of splenectomy on lipid metabolism and inflammatory processes, but further studies (especially molecular levels) are needed to understand the underlying mechanism clearly. In addition, CAIMT measurement via ultrasound after splenectomy may be used as a good option in follow-up for patients, especially those with a high risk of atherosclerosis, cardiovascular and cerebrovascular diseases.

Limitations

The study has certain limitations. First, this is a cohort study. Second, approximately half of the splenectomy group had splenectomy due to autoimmune disease, and this may be a weakness of the study. However, these patients were in remission and were not using any drugs that were effective on atherosclerosis. Third, the number of patients is relatively small. Fourth, we could not analyze the laboratory findings (such as the blood levels of cholesterol, triglyceride, and glucose) that may affect atherosclerosis occurrence. Fifth, we could not examine the underlying mechanism of how splenectomy increases the atherosclerosis process.

CONCLUSION

The CAIMT measurements were higher and therefore atherosclerosis risk was increased in patients with splenectomy. For this reason, it should be kept in mind that these patients may develop cardiovascular and cerebrovascular problems due to atherosclerosis and should be followed up in this respect.

Informed Consent: The aim and content of the research were clarified to the individuals included in the study, and voluntary consent forms were signed.

Author Contributions: OG, MEC, EC, YMB, ET, NTB, CA, CK: Study Design, Data Collection and/or Processing, Analysis and/or Interpretation, Literature Search- OG: Manuscript Preparation, revisions

Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Investigation of the effect of technology and internet addictions on the musculoskeletal system in university students during the post-pandemic period

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ABSTRACT

Objective: The COVID-19 pandemic caused the habits of university students to have spent more time with technological devices and the internet. This study is aimed to investigate the effect of technology and internet addictions of university students on the musculoskeletal (MSK) problems during the post-pandemic period.

Materials and Methods: This cross-sectional study was conducted with 368 university students. The Nordic Musculoskeletal Questionnaire, Pain Numerical Rating Scale, Technology Addiction Scale (TAS), Young's Internet Addiction Test-Short Form (YIAT-SF), and Örebro Musculoskeletal Screening Questionnaire-12-TR (Örebro-12-TR) were applied. Multiple linear regression analysis was performed to assess the effect of technology addiction and internet addiction on the MSK problem.

Results: The mean TAS score of the participants was 45.94±15.46, the mean YIAT-SF score was 24.56±9.52, and the mean Örebro-12-TR score was 35.55±17.14. Technology (p=0.037) and internet addiction (p=0.001) variables had a significant effect on MSK problem. This model can explain 18.4% of the total variance in the risk of developing MSK problems (adjusted R2=0.184).

Conclusion: This study showed that internet and technology addictions affected the MSK problems during the post-pandemic period. Interventions and training programs could reduce the risk of MSK problems.

Keywords: Internet Addiction; Technology Addiction; Musculoskeletal Diseases

INTRODUCTION

Technology and internet addiction are non-substance-related behavioral addictions (1). In general, it can be defined as the inability to stop the excessive use of technology and the internet and the desire to gradually increase the time spent with them, the emergence of feelings such as excessive nervousness, tension, and restlessness in their absence. These addictions negatively affect a person's work, school, and social life (2).

Long-term use of technology leads to postural changes, especially in the upper body and head. Maintaining inappropriate postural changes exposes individuals to cumulative musculoskeletal (MSK) injuries (3). Particularly the use of computers for more than 6 hours increases the risk of MSK injury in different anatomical regions, such as the neck, shoulder, wrist, and head (4). The rapid development of the internet and its use on mobile devices have increased the duration of individuals' use of technological devices and led to physical inactivity in individuals (5). A recent study has reported that MSK disorders are common in high school students and elucidated the relationship between low physical activities and back pain (6). Studies confirm that prolonged static posture and increased muscle load associated with computer use can result in musculoskeletal injuries in the neck, shoulders, back, elbows, and wrists/hands (7, 8). Similar to computer use, using mobile phones and playing digital games can involve continuous grip and repetitive movements of the thumb and fingers and elevate the risk of injury (9, 10). Moreover, due to the COVID-19 pandemic, the habits of university students to carry out their leisure activities have changed, and university students have spent more time with technological devices and the internet. This situation may have caused the development of technology and internet addictions in young people during the COVID-19 pandemic (11). Hence, this study aimed to investigate the effect of technology and internet addictions of university students on the MSK problems during the post-pandemic period.

Research Article

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MATERIAL and METHODs

Study design

This study was a cross-sectional trial. The research data were obtained between September and December 2022 from students studying at Afyonkarahisar Health Sciences University (AFSU). The Clinical Research Ethics Committee of AFSU (2022/6) approved this study, and it was carried out in line with the Helsinki Declaration. The participants were informed about the content of the study, and their written consent was received.

Participants

The study was conducted at AFSU. The research data were collected by the face-to-face questionnaire method. The inclusion criteria for participants were determined as follows: Being between 18-25 years of age and being a student at AFSU. The following exclusion criteria were determined: The presence of any known orthopedic or neurological pathology affecting the MSK, having undergone a surgical procedure related to the upper and lower extremities or spine in the last 6 months, and the presence of any deformity of the upper-lower extremities or spine.

Sample size

The sample size of the study was assessed with G* Power 3.1.9.7. The level of correlation obtained from the sample study was low (r=-0.17) (12). The calculation was made with the formula f2= R2/1-R2 (f2=0.03) using the correlation coefficient in the reference study (13). Accordingly, to achieve a 95% confidence level and 80% power in multiple linear regression analysis, a minimum of 315 participants should be included in the study.

Data collection tools

In the study, a personal information form, the Nordic Musculoskeletal Questionnaire, Pain Numerical Rating Scale, Technology Addiction Scale, Young's Internet Addiction Test-Short Form, and Örebro Musculoskeletal Screening Questionnaire-12-TR were used.

Personal Information Form: This form consists of 7 questions about age, sex, height, weight, body mass index (BMI), technological device (mobile phone, tablet computer, laptop, desktop computer), and internet use.

Nordic Musculoskeletal Questionnaire (NMQ): In this study, the NMQ was used to identify the body region where MSK problems were observed and calculate their frequency. The NMQ is a self-administered questionnaire, which questions MSK problems within 12 months and the resulting work disability. Furthermore, it questions the pain status in the last week. Each item of the questionnaire is responded as yes/no. Turan et al. performed its Turkish validity and reliability study (14).

Pain Numerical Rating Scale (P-NRS): This questionnaire was used to evaluate the intensity of pain arising after participants used a technological device (mobile phone, tablet computer, laptop, and desktop computer) and the internet. The participant was requested to evaluate the intensity of pain between 0 (I never had pain) and 10 (I had unbearable pain) (15).

Technology Addiction Scale (TAS): This scale consists of 24 items and four sub-sections: Website Addiction, Instant Messaging Addiction, Social Network Addiction, and Online Gaming Addiction. Five-point Likert rating (never=1, rarely=2, sometimes=3, often=4, always=5) is used to measure all the items used to assess technology addiction. The lowest score that can be obtained from the scale is 24, and the highest score is 120. Higher scores indicate higher addiction (16).

Young's Internet Addiction Test-Short Form (YIAT-SF): The Internet Addiction Test was developed by Young (1998), and its short form was created by Pawlikowski et al. (17) The scale comprises 12 questions with five-point Likert rating (1=Never, 5=Very often). The lowest score that can be obtained from the scale is 12, and the highest score is 60. High scores indicate that the level of internet addiction is high. Kutlu et al. showed the Turkish validity and reliability of the scale in university students (18).

Örebro Musculoskeletal Screening Questionnaire-12 Turkish Version (Örebro-12-TR): This 12-item self-report questionnaire evaluates all MSK problems, including the spine, upper and lower extremities, and accordingly aims to predict the severity, dysfunction, status of receiving a report, cost and recovery time of the problem (19). Each item takes a value between 0 and 10 according to the response given. Items 8, 11, and 12 are calculated reversely. 120 is the highest score that can be obtained from the questionnaire. A high score obtained from the questionnaire shows that the individual has a high risk of receiving a report due to the MSK disorder, making high health expenditures, and having a high risk for an MSS problem (20).

Statistical Analysis

The data were analyzed with IBM SPSS Statistics 26.0 (SPSS Inc, Chicago, IL, USA) program. A decision was made according to normal distribution, skewness and kurtosis values. Variables with skewness and kurtosis values between -2 and +2 exhibit the characteristics of a normal distribution (21). As a result of the analysis, it was observed that all variables fit the normal distribution. Continuous data were presented as mean and standard deviation, whereas categorical data were presented as numbers and percentages. Multiple linear regression analysis was performed to assess the effect of independent variables (technology addiction and internet addiction) on the dependent variable (MSK problem). Cronbach's alpha coefficient was calculated to assess the internal consistency of the scales used in the study. Cronbach's alpha values of the TAS, YIAT-SF, and Örebro-12-TR were 0.929, 0.922, and 0.735, respectively. The statistical significance level was accepted as $p<0.05$ (22).

RESULTs

The questionnaire was sent to a total of 385 individuals. Twelve individuals disagreed to participate in the study (3.12%), and 5 individuals (1.30%) could not meet the inclusion criteria (2 individuals were >25 years old, and 3 individuals had a problem affecting the MSK). The study was completed with 368 participants (95.58%) (**Figure 1**). The participants' mean age was 19.96±1.42 years. Of the participants, 74.5% were female.

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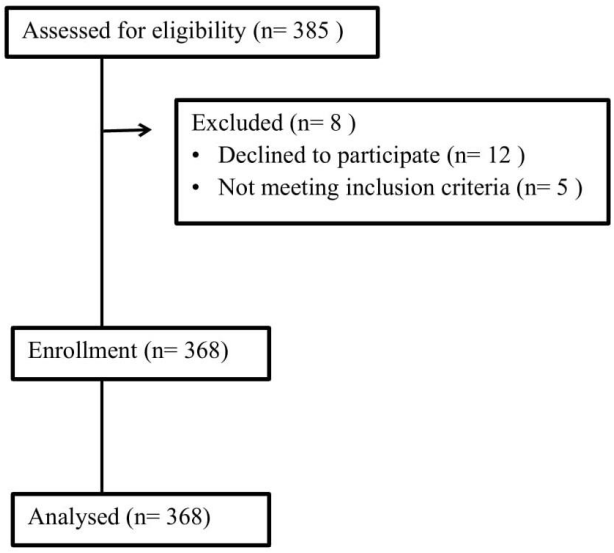

Figure 1. Flowchart of the study

The mean TAS score of the participants was 45.94±15.46, the mean YIAT-SF score was 24.56±9.52, and the mean Örebro-12-TR score was 35.55±17.14. The classifications of the students regarding technology addiction, internet addiction, and MSK problems are presented in **Table 2.**

Multiple linear regression analysis was conducted to examine the effect of technology and internet addiction variables on the MSK problem. The model created according to the analysis results is statistically significant (F=20.218, p<0.001). Technology (p=0.037) and internet addiction (p=0.001) variables included in the model significantly affect the MSK problem. This model can explain 18.4% of the total variance in the risk of developing MSK problems (adjusted R2=0.184) **(Table 3).**

Table 2: Classification of students' technology and internet addiction and musculoskeletal problems

Variables	n(%)
Technology Addiction (scoring) (n=368) (16).	
Not addicted (0-24)	6 (1.6)
Slightly addicted (25-48)	237 (64.4)
Moderately addicted (49-72)	102 (27.7)
Quite addicted (73-96)	20 (5.4)
Highly addicted (97-120)	3 (0.8)
Internet addiction (scoring) (n=368) (17)	
Not addicted (≤37)	338 (91.8)
Addicted (>37)	30 (8.2)
Musculoskeletal problem (scoring) (n=368) (23)	
Low risk (<57)	323(87.8)
Moderate risk (57-72)	33 (9.0)
High risk (>72)	12 (3.3)

Table 1: contains other descriptive variables of the participants.

Variables	
Age (year) (n=368), mean±SD	19.96±1.42
Gender (n=368), n(%)	
Female	274 (74.5)
Male	94 (25.5)
BMI (kg/cm²) (n=368), mean±SD	21.96±3.50
Time spent with technological devices and the internet in a day (min) (n=368), mean±SD	252.02±131,62
Does pain occur at the end of the time spent with technological devices and internet? (n=368), n(%)	
Yes	246 (66,8)
No	122 (33,2)
Distribution of pain at the end of time spent with technological devices and internet (n=368), n(%)	
Neck	238 (64.7)
Shoulders	119 (32.3)
Elbows	23 (6.3)
Wrists/Hands	79 (21.5)
Upper back	132 (35.9)
Low back	110 (29.9)
Hips/ Thighs	24 (6.5)
Knees	14 (3.8)
Ankles/Feet	7 (1.9)
Intensity of pain at the end of time spent with technological devices and internet (n=246), n(%) mean±SD	3.81±1.68
Distribution of those with any problems (pain, discomfort or numbness) at any time in the body parts specified during the last 12 months (n=368), n(%)	
Neck	263 (71.5)
Shoulders	179 (48.6)
Elbows	37 (10.1)
Wrists/Hands	100 (27.2)
Upper back	218 (59.2)
Low back	202 (54.9)
Hips/ Thighs	67 (18.2)
Knees	62 (16.8)
Ankles/Feet	45 (12.2)
Avoided of everyday activities (work, home or leisure) due to pain at any time in the specified body parts during the last 12 months (n=368), n(%)	
Neck	72 (19.6)
Shoulders	39 (10.6)
Elbows	17 (4.6)
Wrists/Hands	26 (7.1)
Upper back	54 (14.7)
Low back	57 (15.5)
Hips/ Thighs	18 (4.9)
Knees	20 (5.4)
Ankles/Feet	20 (5.4)

Table 3. The effect of technology addiction and internet addiction on musculoskeletal problems

Enter Metod	*B*	95.0% Confidence Interval for *B*		SE	β2	t	p	VIF
		Lower bound	Upper bound					
(Constant)	16.957	8.095	18.576	2.665	-	5.004	**<0.001***	-
Technology addiction total score	0.198	0.012	0.384	0.094	0.171	2.097	**0.037***	2.972
Internet addiction total score	0.534	0.233	0.835	0.153	0.283	3.483	**0.001***	2.972

Abbreviations:VIF= Variance Inflation Factor; **B=**Unstandardized Coefficients B; **β2=** Standardized Coefficients **B;** Significant level=*p < 0.05.
Summary of the model: F= 42.249; p<0.001; **R=**0.434; **Adj.R2=**0.184; **SEE=** 16.220; **Durbin-Watson=** 2.073

DISCUSSION

In the present study, university students' technology and internet addictions were researched, and their effects on MSK problems were investigated. Students' technology and internet addictions were found to be at a low level. Students were included in the low-risk group in terms of MSK problems. Moreover, the study showed that technology and internet addictions increased the risk of developing MSK problems. Due to the habits of making use of leisure time, which are predicted to change in university students during the COVID-19 pandemic, there is a need to evaluate students' technology and internet addictions during the post-pandemic period. This study is one of the rare studies investigating the effect of university students' technology and internet addictions on MSK problems during the post-pandemic period.

Modern communication and engagement tools such as video games, social media and online shopping, which young people frequently use nowadays, employ various behavioral techniques to maintain, encourage, and reward frequent use, resulting in addiction (24). The rapid spread of the internet and technological advances in the modern world also contribute to technology and internet addictions (25). Furthermore, students' use of the internet and technological devices (especially smartphones) for purposes such as education, messaging, watching videos, playing games, and using social media accelerated the increase in technology and internet addictions during the COVID-19 pandemic (26). In a study from Bangladesh, a low level of internet addiction was identified in one-quarter of the students, a moderate level of internet addiction was found in more than half, and a high level of internet addiction was determined in 13%. In a study conducted during the pandemic in China, the overall prevalence of internet addiction was 36.7%, and the prevalence of severe internet addiction was 2.8% (27). During the pandemic in Turkey, 4.8% of adolescents had limited internet addiction, and approximately 1% had full addiction symptoms (28). This study was carried out during the post-pandemic period and, unlike other studies, revealed that 9% of university students were internet addicted. Differences between studies may result from the use of different assessment methods, differences between populations, and conducting studies in different periods. However, the internet addiction rate reached in this study was consistent with a study conducted on university students in Turkey prior to the pandemic (9.7%) (29).

In this study, technology addiction was also evaluated with a local scale. According to the results, more than half of the participants had slight technology addiction, one-third had a moderate level of addiction, and approximately one-quarter had a quite/high addiction. Likewise, in a study performed during the pandemic in Turkey, a slight technology addiction was observed in nursing undergraduate students (30).

MSK problems are public health problems that lead to loss of productivity and health expenditures during the treatment process, and they are seen worldwide and in all age groups (31). In this study, students were in the low-risk group in terms of the development of MSK problems. The low internet and technology addiction rate of the Turkish student population in this study may have reduced the risk of MSK. Additionally, university students' most common MSK problems were neck, back, low back, and shoulder problems. The results of this study were similar to studies on the MSK involving university students in the literature (12, 32-35).

In university students, MSK problems arise due to many factors. The present study emphasizes that internet and technology addictions increase the risk of developing MSK problems in university students. The literature focuses mostly on internet addiction (36) and smartphone use regarding MSK problems (12). To spend time on the internet for many reasons such as texting, playing games, watching videos, or social media, students use mobile phones, computers, or laptops for a long time and in a fixed posture (37). Nowadays, university students prefer mobile phones to computers due to the rapid development of mobile phones, their widespread use, availability, and popularity among university students (37). Most studies assert that prolonged stay in a fixed posture with increased neck flexion to see the screen of a smartphone cause cervical and spinal problems (38, 39). According to a study, the use of mobile phones has a higher risk of MSK injury compared to the use of laptops and desktops (40). Working with a laptop on the lap, at an inappropriate table or place causes users to have an inappropriate posture. Repetitive movements in a poor posture result in neck, back, shoulder, and wrist injuries in laptop users (32). According to a study from Hong Kong, university students' poor sitting postures and postures while lying down on one side or face down during the use of electronic devices were associated with MSK injuries (36). In conclusion, studies in the literature support the findings of this study.

The current study has a few limitations. The single-center nature of the study may lead to a selection bias in sample selection. Moreover, in the study, students' income levels, physical activity levels, bag-carrying status, or the posture in which they used technological devices were not taken into consideration.

CONCLUSION

This study showed the effect of internet and technology addictions on MSK problems during the post-pandemic period. This effect can be explained by the prolonged maintenance of a fixed poor posture and repetitive movements while staying in that posture (12, 35, 36). Prolongation of the time spent in front of the screen due to addiction may lead to physical inactivity and pose a risk for MSK problems (40). Also, the fact that the population in this study has a low risk of MSK can be attributed to the low level of internet and technology addiction. Therefore, this study recommends organizing intervention and training programs against internet and technology addictions to reduce the risk of developing MSK problems in students.

Informed Consent: The aim and content of the research were clarified to the individuals included in the study, and voluntary consent forms were signed.

Author Contributions: ETH: Study Design, Data Collection and/or Processing, Analysis and/or Interpretation, Literature Search- **ETH:** Manuscript Preparation, revisions

Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Vitamin D deficiency in healthy adolescents aged 12–17 years in Kirikkale, Turkey

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ABSTRACT

Objective: This study was performed to determine the prevalence of vitamin D deficiency and associated factors in apparently-healthy adolescents in the Central Anatolia region of Turkey where nutritional rickets is common.

Materials and Methods: This prospective cohort study was performed in the Kirikkale province of Central Anatolia, Turkey. Adolescents aged 1 to 17 years old with no health complaints were enrolled between February 2012 and February 2013. Adolescents younger than 12 and older than 17 age, those with chronic diseases, and those using any medications known to affect vitamin D metabolism were excluded. A total of 358 adolescents, consisting of 235 (65.5%) girls and 123 (34.5%) boys with an average age of 14.6 ± 1.58 years, were included in this study. Serum concentrations of 25-hydroxy vitamin D [25(OH)D] and other bone mineralization markers were measured in the summer and winter.

Results: In blood samples, phosphorus (P), alkaline phosphatase (ALP), bone-ALP (B-ALP), parathyroid hormone (PTH), and 25(OH)D levels were considerably lower in female adolescents than in male adolescents. The rate of vitamin D deficiency was higher in girls than in boys. B-ALP level was compared to Vitamin D level in each season; there was no significant relation in winter, but vitamin D level decreased with increasing B-ALP level in summer. B-ALP level was compared to vitamin D level according to sex; there was no significant relation in male adolescents, but vitamin D level decreased while B-ALP level increased in female adolescents.

Conclusion: This study showed that vitamin D deficiency or inadequacy is very common among adolescents, particularly in females in Central Anatolia region of Turkey.

Key words: 25-hydroxy vitamin D, Adolescent rickets, Vitamin D inadequacy, Subclinical vitamin D deficiency, Vitamin D insufficiency

INTRODUCTION

Vitamin D plays a pivotal role as a hormone together with parathyroid hormone (PTH) in regulating calcium (Ca) and phosphorus (P) levels, and therefore, ensuring optimal bone mineralization and metabolic and neuromuscular functions (1, 2). Rickets is the most important result of vitamin D deficiency in children. However, without clinical symptoms of rickets, inadequate vitamin D level is defined by serum 25-hydroxy vitamin D3 (25(OH)D) levels in laboratory tests. The prevalence of vitamin D insufficiency (hypovitaminosis D) or subclinical vitamin D deficiency is estimated to be higher than previously thought, and its incidence is increasing both in Turkey and worldwide (3–8). In vitamin D insufficiency, 25(OH)D levels decrease first, followed by a reduction of intestinal Ca and P absorption. Parathormone and active vitamin D maintain serum Ca levels within the normal range, and clinical and biochemical findings become more apparent during this process. Ultimately, it becomes impossible to maintain Ca equilibrium in vitamin D insufficiency despite PTH and active vitamin D production, with adverse effects on bone metabolism (9).

Vitamin D receptors are present in many tissues, and active vitamin D is synthesized by exposure of the skin to sufficient sunlight. Vitamin D deficiency is a risk factor for the development of several cancers (breast, ovarian, colon, prostate), autoimmune diseases (multiple sclerosis, type 1 and type 2 diabetes mellitus), hyperproliferative skin diseases (psoriasis), hypertension, and infectious diseases. Therefore, maintaining normal vitamin D levels is becoming increasingly important to ensure optimal bone health and prevent chronic diseases (10).

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The present study was performed to determine the prevalence of vitamin D insufficiency in healthy-appearing adolescents, to identify factors involved in vitamin D deficiency, and to demonstrate the effects on bone health in our region where subclinical vitamin D insufficiency is relatively common. This report will provide information about vitamin D insufficiency and/or deficiency to parents and adolescents to prevent vitamin D insufficiency; it will also emphasize the significance of nutrition, sunlight exposure, and physical activity for protection against the effects of vitamin D insufficiency, aid in developing health policy to address vitamin D deficiency, and highlight the need for vitamin D supplementation in high risk subjects.

MATERIAL and METHODs

Adolescents aged 12–17 years old without chronic disorders or on medications and attending primary and secondary schools in the central Anatolian city of Kirikkale, Turkey, were enrolled in this study via a screening study conducted between February 2012 and February 2013. The study was conducted in four phases:

1) identification of the study group;
2) obtaining blood samples and a questionnaire;
3) evaluation of serum samples; and
4) statistical analysis.

Based on the survey data provided by Kirikkale Census Bureau, the population contained 30000 adolescents aged 12–17 years old at the time of the study. Given an estimated vitamin D deficiency incidence rate of 1.67%–19% (7), sample-size calculation indicated that it was necessary to enroll 250–450 adolescents (n=284) in the study. All subjects were selected randomly from different schools and underwent physical examination in the schools according to the study plan. The Tanner staging system was used for the assessment of puberty.

A questionnaire regarding sociodemographic characteristics, dietary habits, sunlight exposure, drug usage, chronic diseases, and physical activity of the subjects was developed. All subjects who agreed to complete the questionnaire after discussing it with their parents/guardians were included in the study. The ethical committee of our institution approved the study (10.05.2012, No: 12/32), and all subjects provided written informed consent. Adolescents using vitamin D and Ca preparations, anticonvulsant agents, corticosteroids, heparin, and estrogen derivatives, which may affect bone metabolism, and those with chronic liver, kidney, endocrine, or gastrointestinal diseases were excluded from the study.

Blood samples were drawn from all subjects into vacuum tubes and EDTA tubes after an overnight fast for biochemical evaluation. Sera were obtained by centrifugation at 3780 rpm for 7 minutes. Serum samples were analyzed at the Biochemistry and Paediatric Metabolism Laboratory of Kirikkale University Medical Faculty, to assess the levels of Ca, P, ALP, B-ALP, vitamin D, and PTH.

Serum calcium levels were assessed using the O-cresolphthalein method, and the results are given as mg/dL. Normal serum total Ca level was defined as 8.8–10.4 mg/dL (37).

Serum phosphorous levels were assessed using the phosphomolybdenum complex method. Normal serum total P level was defined as 2.9–5.4 mg/dL (37).

Serum alkaline phosphatase levels were assessed using the p-nitrophenylphosphate (P-NPP) kinetic method, and the results were given as U/L (37). Normal ALP levels were evaluated according to the age and sex. Bone-specific alkaline phosphatase levels were assessed by enzyme-linked immunosorbent assay (ELISA) using a commercial kit (39).

To evaluate serum 25(OH)D levels, 2 cc of venous blood samples were added to EDTA tubes, centrifuged for 5 minutes at 5000 rpm, and the resulting plasma samples were examined by high performance liquid chromatography (HPLC).

Serum PTH levels were assessed using a chemiluminescent (immunoassay) method, and the results were given as pg/mL. Normal serum PTH level was defined as 12–65 pg/mL.

Statistical analyses were performed using SPSS version 20.0. Quantitative variables are expressed as means±standard deviation (SD), while qualitative variables are expressed as percentages. Independent samples, t-test, and chi-square test were used for comparisons, as appropriate. Spearman's correlation test was used to assess correlations between parameters. In all analyses, $p<0.05$ was taken to indicate statistical significance.

RESULTs

A total of 358 subjects from six different schools met the inclusion criteria and completed the study. The study population consisted of 235 (65.6%) girls and 123 (34.4%) boys with a mean age of 14.6±1.58 years, ranging from 12 to 17 years. The ratio of girls/boys was 1.9.

Biochemical values relevant to our investigation are shown in **Table 1**.

Table 1. Biochemical values (mean±SD)

	Whole group n=358	Girls n=235	Boys n=123	*p*-value boys vs. girls
Ca	9.96±0.389 mg/dL	9.968±0.386	9.966±0.376	>0.05
P	3.94±0.663 mg/dL	3.816±0.614	4.198±0.683	>0.05
ALP	147.23±89.328 U/L	111.62±58.29	215.26±98.6	>0.05
B-ALP	64.38±46.11 µg/L	46.706±34.27	98.00±47.26	>0.05
25(OH)D	20.86±10.97 ng/mL	19.88±11.04	22.987±10.509	>0.05
PTH	48.62±24.04 pg/mL	46.0.88±19.64	53.524±30.318	>0.05

Ca, calcium; P, phosphorus; ALP, alkaline phosphatase; B-ALP, bone alkaline phosphatase; PTH, parathormone.

Mean levels of Ca, P, ALP, B-ALP, PTH, and 25(OH)D3 were significantly lower in adolescent girls than in adolescent boys ($p<0.05$) (**Table 2**).

The prevalence of vitamin D insufficiency, defined according to the accepted vitamin D levels in Europe, was high in our population and was more common among girls than boys (41).

- Deficiency: serum 25(OH)D3 level BELOW 10 ng/mL
- Inadequate: serum 25(OH)D3 level BETWEEN 10 and 25 ng/mL
- Adequate: serum 25(OH)D3 level ABOVE 25 ng/mL (**Table 2**)

The USA Institute of Medicine (IOM) adjusts the following guidelines for serum 25(OH)D levels (42) (**Table 3**).

- Deficiency: serum 25(OH)D3 level BELOW 20 ng/mL
- Inadequate: serum 25(OH)D3 level BETWEEN 20-30ng/mL
- Adequate serum 25(OH)D3 level ABOVE 30 ng/mL

Vitamin D levels were lower in adolescents 12–14 years old than in those 15–17 years old although the difference was not significant ($p>0.05$) (**Table 4**).

Assessment of the relationship between sex and physical activity indicated that the number of adolescents who did not participate in sporting activities was higher in girls than in boys (60.7% vs. 24.4%, respectively). Adolescents with lower levels of physical activity showed reduced vitamin D levels. There was a non-significant difference in serum vitamin D levels related to physical activity between boys and girls.

A positive correlation was found between mean Ca level and household income (**Table 5**).

Ca levels were higher in adolescents whose mothers were employed than in those whose mothers did not work outside the home ($p>0.05$).

B-ALP levels were compared with seasonal vitamin D levels, and the results indicated that there was no significant relation in winter, while there was an increase in B-ALP levels with decreasing vitamin D levels in summer. B-ALP levels were compared to vitamin D levels in both sexes, and the results indicated that there was a significant increase in B-ALP levels with decreasing vitamin D levels in adolescent girls, while there was no significant relation in adolescent boys (**Table 6**).

Season, age, parental educational status, mother's employment status, socioeconomic status, dietary habits, pubertal stage, mode of dressing in girls, physical activity, duration of sun exposure, and body mass index had no effect on vitamin D level. No associations were detected between vitamin D levels and those of Ca, P, ALP, or PTH.

Table 2. Accepted vitamin D levels according to the Ministry of Health, Turkey (31-33, 38)

	Group n (%)	Girls n (%)	Boys n (%)	*p*-value boys vs. girls
Deficiency: <10 ng/mL	46 (12.8%)	37 (15.7%)	9 (7.3%)	>0.05
Inadequate: 10–25 ng/mL	204 (57%)	131 (55.7%)	73 (59.3%)	>0.05
Adequate: >25 ng/mL	108 (30.2%)	67 (28.5%)	41 (33.3%)	>0.05

Table 3. Accepted 25(OH)D serum levels according to USA IOM guidelines (40)

	Group n (%)	Girls n (%)	Boys n (%)	*p*-value boys vs. girls
Deficiency: <20 ng/mL	183 (51.1%)	137 (58.3%)	46 (37.4%)	>0.05
Inadequate: 20–30 ng/mL	112 (31.3%)	60 (25.5%)	52 (42.3%)	>0.05
Adequate: >30 ng/mL	63 (17.6%)	38 (16.2%)	25 (20.3%)	>0.05

Table 4. Comparison of Vitamin D levels according to age

Age (year)	Mean±SD (ng/mL)	Minimum (ng/mL)	Maximum (ng/mL)	*p*-value
12 (n=44)	19.85±9.78	3.76	57.57	p>0.05
13 (n=52)	19.78±9.41	8.64	44.99	p>0.05
14 (n=72)	21.14±11.30	4.20	63.04	p>0.05
15 (n=71)	20.30±10.41	3.53	48.07	p>0.05
16 (n=66)	20.91±13.02	4.68	76.15	p>0.05
17 (n=49)	23.23±10.93	4.91	57.40	p>0.05

Table 5. Income classes and mean serum Ca levels (mean±SD)

Income class (TL/month*)	Group Ca (mg/dL)	Minimum Ca (mg/dL)	Maximum Ca (mg/dL)	*p*-value
High (213)	9.993±0.356	8.90	11.00	>0.05
Medium (117)	9.956±0.417	9.19	11.50	>0.05
Low (28)	9.802±0.468	8.14	10.61	>0.05

Table 6. Relationship between gonadal for B-ALP and vitamin D levels

B-ALP	Group B-ALP	Minimum	Maximum	*p*-value
Girls (235)	20.08±11.47	4.20	76.15	**<0.05**
Boys (123)	22.63±10.73	15.65	63.04	>0.05

DISCUSSION

Adolescence is a critical period for bone health in adulthood. In this period, the risk of vitamin D insufficiency is increased due to accelerated bone development. Vitamin D deficiency and/or insufficiency are important health issues that affect not only infants but also +adolescents (30). There is still no absolute consensus as to what a normal range for 25(OH)vit D. However, recently, are being agreed that by most experts/scientists, vitamin D deficiency should be defined as a 25(OH)D of <20 ng/mL. Vitamin D insufficiency is now accepted as a 25(OH)D of 21-29 ng/mL. Thus, despite the lack of rickets in both developed and developing countries, the high incidence rates of vitamin D deficiency and/or inadequate vitamin D levels in the adolescent period have attracted a great deal of attention (7).

There have been few studies in Turkey regarding vitamin D levels in adolescents. In a study performed in Van province, Acar et al. reported a rate of vitamin D insufficiency of 52.4% among adolescents (11). Hatun et al. reported inadequate levels of vitamin D and vitamin D deficiency in 43% and 21.3% of 89 adolescent girls, respectively (12). In a study by Budak et al., vitamin D level was found to be <16 ng/mL in the majority of 69 female university students in a reproductive age (13). Demirçeken et al. reported a 13-year-old adolescent with rickets who presented with hypocalcemic tetanus due to vitamin D deficiency caused by limited sunlight exposure (14). In our study, the rates of inadequate vitamin D level and vitamin D deficiency were 57% and 12.8% among the adolescents in Kirikkale. One of the latest studies conducted by Karagüzel et al. on vitamin D status in Turkey showed that the proportion of vitamin D deficiency (<20 ng/mL) in adolescents was 82%, and girls had lower 25(OH)D levels than boys in northeastern Turkey (24). Vitamin D level above 25 ng/mL (normal) was seen in 30.2% of the subjects. Based on the European vitamin D level classification, vitamin D deficiency (or)(<20 ng/mL) and vitamin D insufficiency (20–30 ng/mL) were seen at rates of 51.1% and 31.3%, respectively, in the adolescents from Kirikkale. Vitamin D level was >30 ng/mL (normal) in 17.6% of the adolescents included in the present study.

Nutritional rickets is more common in boys during infancy (15), while the risk is higher for girls during adolescence (3). In previous studies, the rate of vitamin D deficiency was higher in adult women than in adult men (34,35). Narchive et al. reported that 95.2% of patients diagnosed with adolescent rickets in Saudi Arabia were girls (16), while Rajeswari et al. reported that all patients diagnosed with symptomatic rickets in India were girls (17). Moussavive et al. reported vitamin D deficiency rates of 72.1% in girls and 18.3% in boys, indicating a fourfold higher incidence of vitamin D deficiency in girls (18). In our study, the mean vitamin D level was 19.7±11.03 ng/mL in adolescent girls, while that in adolescent boys was 22.9±10.5 ng/mL ($p<0.05$). Conversely, Chapuy et al. reported that age and sex had no effect on serum 25(OH)D levels in a study performed in 1596 volunteers from nine geographic regions in France (19). Our study showed no significant association between age and vitamin D level in adolescence. However, vitamin D insufficiency and deficiency were more common in adolescents at 12–13 years old, when puberty is accelerated. This finding emphasized the importance of diagnosis and treatment of inadequate vitamin D level and/or deficiency in the early adolescent period in terms of bone development during subsequent years.

Therefore, it is recommended to initiate prophylaxis in the early period of adolescence due to the effects of vitamin D on subsequent life.

In a study in Izmir, Ölmez et al. reported that vitamin D levels were low in adolescents whose parents have low educational status (13). Bener et al. (20) found no associations between vitamin D level and parental educational status, employment status, or occupation in a study comparing cases with vitamin D deficiency to those with normal vitamin D levels. Our study found no significant associations between parental educational status and inadequate, deficient, or normal vitamin D levels ($p>0.05$).

In the present study, Ca levels were significantly higher in adolescents whose mothers were employed compared to those not working outside the home ($p<0.05$), suggesting higher awareness regarding nutrition among employed mothers. In addition, we speculated that the children of these mothers may be playing outside more frequently and, expose to the sun light more. Narchi et al. (16) reported that risk factors for rickets included insufficient intake of Ca (490 mg/day) and vitamin D (2.8 µg/day) from foods, as well as consumption of carbonated beverages with high P contents. In our study, no significant associations were found between adolescents' dietary habits and vitamin D deficiency, insufficiency, or normal vitamin D levels ($p>0.05$).

A previous study indicated an association between socioeconomic status and vitamin D level in adolescents, with low socioeconomic status being a significant risk factor for vitamin D deficiency (21). In our study, however, there was no significant association between income and vitamin D deficiency ($p>0.05$). Similarly, Hatun et al. also reported that socioeconomic status had no effect on vitamin D levels (12).

However, Ca levels were significantly increased in adolescents from households with higher income levels ($p<0.05$). This finding suggests that increased income also increases consumption of calcium-rich foods.

Narchi et al. (16) reported that the daily duration of sunlight exposure was less than 60 minutes in all 21 cases diagnosed with adolescent rickets and less than 30 minutes in three-quarters of these cases. In our study, there were no significant associations between the duration of sunlight exposure and vitamin D deficiency and/or insufficiency ($p>0.05$).

In our study, no significant association was detected between physical activity and vitamin D level ($p>0.05$). However, adolescent boys showed a significantly higher rate of participation in sports activities than girls ($p<0.05$). This suggests that adolescent girls with limited physical activity are at higher risk of vitamin D deficiency and/or insufficiency. In a study performed in a population of 89 girls aged 13–17 years old, Hatun et al. found that vitamin D levels were lower in girls who dressed conservatively due to religious and traditional demands. The authors found inadequate vitamin D levels in 70% of these girls and vitamin D deficiency in 30% of girls who dressed conservatively, and that vitamin D levels were significantly lower in girls who

dressed conservatively compared to those who dressed more liberally (12). Ergür et al. reported lower vitamin D levels in infants of mothers who dressed conservatively (23). These studies emphasize the influences of clothing and sunlight on vitamin D levels. Acar et al. reported that vitamin D levels were lower in girls who dressed conservatively, but there was no significant association between clothing style and incidence of adolescent rickets (11). In our study population, 94.5% of adolescent girls dressed liberally whereas 5.5% dressed conservatively. There was no significant relation between clothing style and vitamin D levels in our study ($p>0.05$). However, this may have been due to bias caused by the lower number of adolescents who dressed conservatively.

Narchive et al. reported that all of 21 cases with adolescent rickets were in Tanner II and IV pubertal stage (16). However, we found no significant association between the pubertal stage and vitamin D in the present study ($p>0.05$).

Low Ca and high ALP levels are anticipated in classical nutritional rickets (15). However, 25(OH)D, Ca, P, and ALP levels were measured in a study of 193 cases, but low Ca and P levels as well as high ALP levels were not detected in any of the subjects with inadequate vitamin D levels (11). The authors suggested that 25(OH)D level should be determined in patients with risk factors who are thought to have vitamin D deficiency or insufficiency clinically even if their serum Ca, P, and ALP levels are normal (25). In another study, no changes were detected in serum Ca, P, and ALP levels in relation to vitamin D deficiency and inadequacy (20). Moreover, in another study, PTH levels remained within the normal range in adolescents with insufficient vitamin D stores at the end of winter, suggesting a distinct mechanism for maintaining normal PTH levels (26). In our study, no significant associations were detected between vitamin D level and Ca, P, ALP, or PTH.

In adults with normal liver function, 50% of total ALP originates from bones, while B-ALP accounts for 90% of total ALP in children and adolescents due to accelerated bone mineralization (27). Therefore, it is recommended to determine B-ALP for the assessment of bone turnover. However, a study performed on 382 children indicated that B-ALP levels were normal in 92% of children despite the detection of vitamin D levels <20 ng/mL in 25% of the children (28). Similarly, no significant association was detected between vitamin D level and B-ALP ($p>0.05$) in our study. However, the mean B-ALP level was found to be significantly higher in adolescent girls with vitamin D deficiency and/or inadequacy in winter ($p<0.05$). Abdullah et al. (29) suggested that there were no clinical findings of rickets in adolescents with rickets and that the most common complaint was a pain in the lower extremities. In our study, there were musculoskeletal complaints in 7% of cases, with the remaining 93% of the adolescents in the study showing no musculoskeletal complaints. Thus, there was no significant association between vitamin D levels and musculoskeletal complaints ($p>0.05$).

In conclusion, vitamin D deficiency and inadequate vitamin D levels were detected in 37 (15.7%) and 131 (55.7%) of 235 girls and in 9 (7.3%) and 73 (59.3%) of 123 boys included in this study, respectively, according to the criteria of the Turkish Republic Ministry of Health despite the subtropical climate and abundant sunlight in our country. Using the European vitamin D limits in our study, we found vitamin D deficiency and inadequate vitamin D levels in 60 (25.5%) and 137 (58.3%) of the girls and in 46 (37.4%) and 52 (42.3%) of the boys, respectively, indicating that low vitamin D status is a serious problem in Turkey. Results suggest that vitamin D intervention, which is a safe and non-invasive treatment, may exert a potential benefit in reducing the severity of COVID-19 infection (43). Vitamin D deficiency or inadequate vitamin D levels may increase the incidence of intrauterine growth retardation, premature birth, and congenital rickets at the time of birth. In addition, given the positive effects in reducing the risks of multiple sclerosis, hypertension, type 1 and 2 diabetes, asthma, and colon, prostate, breast, and ovarian cancer, it is becoming increasingly clear that sufficient levels of vitamin D in childhood and adolescence are essential for health.

CONCLUSION

When assessing vitamin D, geographic location, climate, lifestyle, and dietary habits should be determined, and vitamin D supplementation should be planned according to the results. This approach will prevent unnecessary diagnosis and treatment as well as vitamin D intoxication. Our results indicated that it is appropriate to use prophylactic vitamin D dosages determined according to the conditions in Turkey. Information about inadequate and/or deficient vitamin D levels should be provided to parents and adolescents to prevent vitamin D insufficiency. This important health issue can be ameliorated by emphasizing the significance of proper nutrition, sunlight exposure, and physical activity for protection against vitamin D insufficiency. It is necessary to develop a health policy to address vitamin D deficiency and to emphasis the need for vitamin D supplementation in adolescents.

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Evaluation of the characteristics of the patients Hospitalized in the internal diseases clinic in a third-level hospital a single-center experience

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ABSTRACT

Objective: General internal medicine clinics are units where patients are evaluated holistically and systematically by working together with other branches of specialization. In the present study, the purpose was to reveal the general internal medicine practice by examining the characteristics and reasons for the hospitalization of patients in the general internal medicine clinic of a third-level university hospital.

Material and Methods: The data of patients who were hospitalized between 01.10.2020 and 01.10.2022 in Afyonkarahisar Health Sciences University, Faculty of Medicine, Internal Medicine Clinic, General Internal Medicine Ward were obtained. The demographic data, reasons for hospitalization, and hospitalization areas of the patients were examined.

Results: A total of 714 patients were included in the present study. The mean age of the patients was 59.9. The most common reason for hospitalization was symptomatic anemia and malignancy screening. Although symptomatic anemia was the most common reason for hospitalization over 65 years of age, intoxications were observed in patients under 65 years of age and the most common reason for hospitalization from the emergency units was acute pancreatitis, the most common reason for hospitalization from clinics was malignancy examination.

Conclusion: General internal medicine clinics have a wide spectrum in terms of hospitalization causes. The most common reasons for admission to these units are anemia, malignancy examination, and electrolyte disorders.

Keywords: internal medicine, inpatient, anemia

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INTRODUCTION

Internal medicine clinics are units where many chronic diseases are followed up. These clinics play important roles in diagnosing and treating pathologies involving almost all internal organs. Polyclinic, service, and consultation services are provided in these units for patients from the age of 18 on a wide age spectrum, including the geriatric population.

Today, with the increased branching in medicine, the local perspective on the patient has come to the forefront, and the general and holistic approach to diseases has decreased. General internal medicine clinics work together with other specialties and approach patients and diseases with a holistic aspect. In the present study, the purpose was to evaluate the demographic characteristics, reasons for hospitalization, and hospitalization units of the patients hospitalized in a tertiary hospital's general internal medicine clinic, and to reveal the general internal medicine practice.

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MATERIAL and METHODs

The information of the patients who were hospitalized between 01.10.2020 and 01.10.2022 in Afyonkarahisar Health Sciences University, Faculty of Medicine, Internal Medicine Clinic, General Internal Medicine Ward were scanned from the hospital electronic file system. The age, gender, reasons for hospitalization, and hospitalization units (i.e., emergency units, outpatient clinics, etc.) of these patients were reached and evaluated.

According to the definition by the World Health Organization (WHO), a hemoglobin value of <12 g/dl in women and <13 g/dl in men is accepted as anemia (1). Hemoglobin <10 and resting tachycardia and dyspnea because of anemia were evaluated as symptomatic anemia. The patients who applied after taking high-dose drugs for suicidal purposes, and patients with symptomatic complaints after eating mushrooms were considered intoxicated.

Statistical analysis: The SPSS 26.0 (IBM Corp. 2019 IBM SPSS Statistics for Windows, version 26.0. Armonk, NY: IBM Corp.) program was used for statistical evaluations.

RESULTs

A total of 714 patients were included in the study. Among these, 328 (46%) were male and 386 (54%) were female. The youngest of the patients was 18 years old, and the oldest was 93 years old. Although the mean age of women was 58.90, it was 60.01 in men. The overall mean age was found to be 59 years. The age-gender distribution of the patients who were under 65 years of age and over is given in Table 1 (**Table 1**).

When the reasons for the hospitalization of the patients were examined, it was seen that the most common reason was symptomatic anemia in 101 (14.1%) patients. It was found that the most common reason for hospitalization in patients under 65 years old was intoxication with 62 people (8.7%), and hospitalizations for symptomatic anemia with 52 people (7.3%) in people over 65 years of age. The reasons for the hospitalization of the patients are given in Table 2 (**Table 2**)

Distribution of patients hospitalized with electrolyte imbalance:Among the 60 patients, 23 (38%) were hospitalized with hyponatremia and 19 (31%) with hypercalcemia.

Among the 60 patients who were hospitalized because of infection, the most common reason for hospitalization was pneumonia with 22 patients (36%), and urinary system infections were in second place with 19 people (31%).

Regarding the hospitalization units of the patients, it was found that 363 patients (50.8%) were hospitalized by the emergency department, 322 patients (45%) from the outpatient clinic, and 29 patients (4.2%) from other wards and intensive care units. Although acute pancreatitis was the most common diagnosis of hospitalization in the emergency department, it was found that the most common malignancy examination patients were admitted to the outpatient clinic. The distribution of the reasons for hospitalization according to the hospitalized units is given in Table 3 (**Table 3**).

Table 1: The age and gender distribution of the patients who were included in the study

	<65 YEARS OF AGE (N, %)	>65 YEARS OF AGE (N, %)	TOTAL (N,%)
MALE	167 (50.9%)	161 (49.1%)	328
FEMALE	204 (52.8%)	182 (47.2%)	386
TOTAL	371 (52%)	343 (48%)	714

Table 2: The frequency of hospitalization reasons

REASON FOR ADMISSION	<65 YEARS OF AGE (N. %)	>65 YEARS OF AGE (N. %)	TOTAL (N. %)
Acute kidney failure	19 (2.7)	46 (6.4)	65 (9.1)
Adrenal Insufficiency	9 (1.3)	1(0.1)	10 (1.4)
Acute gastroenteritis	8 (1.1)	2 (0.3)	10 (1.4)
Acute cholecystitis	9 (1.3)	5 (0.7)	14 (2)
Acute pancreatitis	53 (7.4)	32 (4.5)	85 (11.9)
Acid etiology	4 (0.6)	3 (0.4)	7 (1)
DM Regulation	38 (5.3)	22 (3.1)	60 (8.4)
Electrolyte imbalance	22 (3.1)	38 (5.3)	60 (8.4)
Infection	25 (3.5)	35 (4.9)	60 (8.4)
General condition disorder	1 (0.1)	7 (1)	8 (1.1)
GI bleeding	15 (2.1)	20 (2.8)	35 (4.9)
Hepatic encephalopathy	1 (0.1)	3 (0.4)	4 (0.6)
Hyperbilirubinemia	3 (0.4)	6 (0.8)	9 (1.3)
Hypertensive attack	0 (0)	8 (1.1)	8 (1.1)
Hypervolemia	2 (0.3)	9 (1.3)	11 (1.5)
Intoxication	**62 (8.7)**	3 (0.4)	65 (9.1)
LFT elevation	7 (1)	1 (0.1)	8 (1.1)
Malignancy screening	44 (6.2)	50 (7)	94 (13.2)
Symptomatic anemia	49 (6.9)	**52 (7.3)**	**101 (14.1)**
TOTAL	371 (52)	343 (48)	714

*DM: diyabetes mellitus, GI bleeding: gastrointestinal bleeding, LFT: liver function tests

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Table 3: The distribution of the hospitalization reasons of patients according to hospitalization units

REASON FOR ADMISSION	EMERGENCY UNIT	POLYCLINIC	CYCLE	TOTAL
Acute kidney failure	43(66.1)	21(32.3)	1(1.6)	65(100)
Adrenal Insufficiency	-	10(100)	-	10(100)
Acute gastroenteritis	2(20)	8(80)	-	10(100)
Acute cholecystitis	9(64.2)	5(35.8)	-	14(100)
Acute pancreatitis	**80(94.1)**	4(4.7)	1(1.2)	85(100)
Acid etiology	-	7	-	7(100)
DM Regulation	7(11.7)	51(85)	2(3.3)	60(100)
Electrolyte imbalance	42(70)	16(26.7)	2(3.3)	60(100)
Infection	17(28.3)	36(60)	7(11.7)	60 (100)
General condition disorder	4(50)	4(50)	-	8(100)
GI bleeding	35(100)	-	-	35 (100)
Hepatic encephalopathy	2(50)	-	2(50)	4(100)
Hyperbilirubinemia	6(66.6)	2(22.2)	1(11.1)	9 (100)
Hypertensive attack	1(12.5)	7(87.5)	-	8 (100)
Hypervolemia	1(9.3)	8(72.7)	2(18.1)	11(100)
Intoxication	54(83.2)	4(6.1)	7(10.7)	65(100)
LFT elevation	3(37.5)	3(37.5)	2(25)	8 (100)
Malignancy screening	13(13.8)	**79(84)**	2(2.2)	94(100)
Symptomatic anemia	44(43.5)	57(56.5)	-	101(100)
TOTAL	363(50.8)	322(45)	29(4.2)	714(100)

*DM: diyabetes mellitus, GI bleeding: gastrointestinal bleeding, LFT: liver function tests

DISCUSSION

Internal medicine clinics are important units where patients with multiple chronic diseases and metabolic and infectious disorders are treated. The practice of general internal medicine clinics has started to change with the increased sub-branches and specializations. General internal medicine clinics aim to maintain a multisystem and holistic approach to the patient and to work in coordination with the branches to ensure the highest efficiency. The present study aimed to reveal the general internal medicine practice by examining the patients hospitalized in the general internal medicine clinic in a third-level university hospital.

In a study examining the patients hospitalized in the general internal medicine clinic that was conducted by Karahan I and Çiftçi A, the average age of the patients was found to be 71, and diabetic problems, electrolyte imbalance, and anemia were found to be the most common reasons for hospitalization (2). In another study examining 262 patients hospitalized in the internal medicine clinic during the pandemic period, the mean age of the patients was found to be 63.3, and the rate of patients over 65 was 57%. In the same study, the most common reason for hospitalization was found to be gastrointestinal bleeding, followed by anemia testing and malignancy screening patients, respectively (3). In the present study, the mean age of the patients was 59, and anemia and malignancy were the most common reasons for hospitalization. The study is similar to other studies in the literature regarding the reason for hospitalization.

Individuals who are over the age of 65 are defined as old by the World Health Organization, and individuals over the age of 85 are defined as very old (4). Internal medicine clinics are polyclinics where the geriatric population is frequently hospitalized for treatment purposes. In a previous study conducted by Nalbant A et al. examining the diagnostic distribution of patients over the age of 65 hospitalized in the general internal medicine clinic, it was reported that the most common diagnosis for hospitalization was symptomatic anemia with a rate of 60% (5).

In another study conducted by Kilit et al. in which geriatric patients who were hospitalized in the internal medicine clinic were evaluated, the most common causes of hospitalization were found to be hyperglycemia and anemia (6). In the present study, the most common reason for hospitalization in individuals over 65 years of age was found to be symptomatic anemia, in line with the literature data, and electrolyte imbalance ranked second.

It was seen in the present study that the most common reason for hospitalization in individuals under the age of 65 was intoxication (i.e., fungi, and suicidal drugs). Intoxication is exposure to an agent that may cause dysfunction in a living organism. Cases of intoxication constitute approximately 0.46-1.57% of all the diagnoses on admission to the emergency department (7). This patient group is admitted to general internal medicine clinics, anesthesia, and psychiatry clinics. In a study examining the patients hospitalized in the general internal medicine clinic conducted by Karahan I and Çiftçi A, patients hospitalized with the diagnosis of intoxication made up 1.6% of the total patients (2). In the present study, it made up approximately 9%. This difference is because of the lack of a clear consensus on the department where these patients will be hospitalized.

Internal medicine clinics admit patients through consultation from the emergency and external wards or polyclinics. In previous studies, internal medicine clinics were found to be at the forefront of the departments where consultation is requested the most from emergency units (8, 9). In the present study, 50.8% of patients hospitalized in the general internal medicine clinic were hospitalized from the emergency units and 45% from the polyclinics. It was also found that the most common reason for hospitalization from the emergency units was acute pancreatitis, and the most common reason for hospitalization from the outpatient clinic was a malignancy examination.

CONCLUSION

As a result, symptomatic anemia and malignancy test patients are among the leading causes of hospitalization of patients who are hospitalized in the general internal medicine clinic. More comprehensive and multicenter studies are needed to determine general internal medicine practice.

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Iron transportation proteins Hepcidin and Ferroportin and alterations in depressive and anxiety disorders

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ABSTRACT

Objective: Iron element has critical roles such as myelin synthesis and neurotransmitter synthesis. Critical enzymes and proteins strictly control iron metabolism. Alterations in the enzyme activities could modify iron metabolism. Metabolic and endocrine changes may influence iron turnover in patients with major depression and anxiety disorders.

Materials and Methods: 30 patients with major depressive disorder (MDD), 30 with anxiety disorders (ADs) according to the DSM 5 criteria, and 30 healthy controls were included. Hamilton Depression and Anxiety Scales were the clinical evaluation tools. Blood samples were collected 12 hours of fasting. Hepcidin and Ferroportin levels were measured with ELISA method.

Results: Both Hepcidin and Ferroportin levels were lower in the MDD group compared to the ADs group, Hepcidin levels were found to be statistically significantly lower ($p= 0.014$). In addition, an inverse correlation was observed between the Hamilton Depression Scale score and Ferroportin levels ($r= -0.214$, $p<0.05$).

Conclusion: Decreased Hepcidin and Ferroportin levels indicate metabolic effects in patients with MDD and disruption of the feedback mechanism between the two proteins. Considering the long duration of the disease in the MDD group in our study, the treatment period was also thought to be prolonged and the use of antidepressants might affect negative feedback.

Keywords: Anxiety disorders, depressive disorder, Ferroportin, Hepcidin

INTRODUCTION

Major Depressive Disorder (MDD) affects more than 264 million people annually (1). The World Health Organization (WHO) has positioned MDD as the third cause of worldwide disease burden and predicted that it will rank first by 2030 (2). Similarly, it is known that anxiety disorders are also commonly seen and their frequency tends to increase (3). In anxiety disorders and MDD, emotional, cognitive, psychomotor, and somatic symptoms can be seen (4). The contribution of neuroendocrine and biochemical processes to clinical processes may lead to metabolic abnormalities that may affect the clinical course. For example, problems such as activation in the hypothalamic-pituitary-adrenal axis, inflammatory activation, and oxidative stress may become evident during depressive periods (5). All these processes together can lead to an increase in morbidity and mortality directly or indirectly, in anxiety disorders and MDD. Many studies have observed that the frequency of diseases such as cardiovascular diseases, diabetes mellitus, and cancer is increased in anxiety disorders and MDD, and occurs at an earlier age (6-8).

It is known that the iron element has critical roles in myelin synthesis, neurotransmitter synthesis, and oxygen transport; and these roles are affected by inflammation (9). Hepcidin is a peptide that plays an active role in iron metabolism and is synthesized from the liver. It plays a regulatory role in the iron release from liver storage, absorption of iron in the diet, and iron release from macrophages (10). Hepcidin performs this regulatory role through Ferroportin. Only one protein allows iron to get out from iron-transferring cells (enterocytes, hepatocyte macrophages), and this protein is called Ferroportin. In other words, Hepcidin reduces iron release into plasma by binding to Ferroportin and causing down-regulation of Ferroportin (11).

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An increase of IL-6, in cases of infection or inflammation, will cause an increase in Hepcidin synthesis, and an increase in iron-loaded macrophages by down-regulation of Ferroportin. This will lead to a decrease in plasma iron and hypoferremia within hours, and the pathogen entering the body will be unable to find iron for use (12). Also, it may cause the development of anemia due to inflammation by stimulating iron-restricted erythropoiesis (13). Similar changes occur in all iron metabolisms in conditions such as inflammation, mitochondrial disorders, and gene mutations. These changes also contribute to the progression of neurotoxic and neurodegenerative processes.

This study aims to evaluate the Ferroportin and Hepcidin levels in major depression and anxiety disorders. In the literature review, no clinical research was found that evaluated Hepcidin and Ferroportin levels in patients with anxiety disorders and/or major depression. It is thought that iron metabolism also plays a role in the multifactorial etiopathogenesis of the aforementioned diseases along with many metabolic disorders. Therefore, changes are possible in Hepcidin and Ferroportin levels and the balance of the feedback axis between them. In our study, we hypothesized that similar to the inflammatory response in patients with major depression and anxiety disorder, Hepcidin levels might be altered, and Ferroportin levels would subsequently be influenced.

MATERIAL and METHODs

Ethics committee approval was obtained from the Afyonkarahisar Health Sciences University (AFSU), Clinical Research Ethics Committee in 03.01.2020 with the number 2020/51. Written informed consent was prepared according to the principles of the Declaration of Helsinki before the study obtained from all participants included in the study. A total of 84 patients, aged between 18-65, who were admitted to the AFSU Faculty of Medicine, Department of Psychiatry Outpatient Clinic consecutively between 01.02.2020 and 01.08.2020, and who were diagnosed with major depression or anxiety disorder according to DSM-5, and were receiving outpatient treatment were included in the study. However, according to the exclusion criteria, 13 people were excluded from the study due to acute infection and 11 people due to anemia. The study was completed with the remaining 60 patients and 30 healthy controls who voluntarily agreed to participate.

Exclusion criteria

- Severe organ failure,
- Alcohol/substance usagewithin last 3 months,
- Use of antioxidants,
- Active infection or have had any infectious disease within last 1 month,
- BMI lower than 18.5 or higher than 24.9,
- Chronic systemic disease (cardiologic, endocrinologic, allergic, genetic, neurologic),
- Received iron replacement therapy within last 3 months,
- Have had severe bleeding that caused significant blood loss within last 3 months, women with menstrual irregularities and excessive bleeding,
- A history of head trauma or brain surgery,
- Had a psychiatric diagnosis other than major depression or anxiety disorder according to DSM-5,
- Pregnancy
- The patien who did not accept participation after reading the detailed explanation of information form.

In addition to the above-mentioned exclusion criteria, subjects in the control group were also excluded if they or a first-degree relative had an axis 1 disorder according to the DSM-5 diagnostic criteria.

The patients diagnosed with major depression or anxiety disorder and the healthy control group included in the study applied Hamilton Depression Rating Scale (14, 15), Hamilton Anxiety Rating Scale (16, 17), and sociodemographic data form, after the clinical interview structured according to SCID-5 was performed in order to determine the clinical status.

Biochemical Measurement Processes

The blood samples required for the study were taken from the antecubital vein in the morning after 12-hour fasting. Complete blood count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), bilirubin, direct bilirubin, indirect bilirubin, albumin, total protein, serum iron, total iron-binding capacity, unsaturated iron-binding capacity (UIBC), ferritin values were measured from the blood samples. For the analysis of Hepcidin and Ferroportin levels: serum samples obtained by centrifugation for 5 minutes at 3220 g of blood taken, were stored in special boxes at -80 °C. and analyzed collectively. When the analyses were performed, the samples were thawed appropriately and reached room temperature in the laboratory of the biochemistry department of the university where the authors were working. In all samples, serum Hepcidin and Ferroportin levels were studied together at the same time. Hepcidin and Ferroportin measurements in serum were made with SunRed branded Human Hepcidin and Ferroportin Elisa kits (Jufengyuan Road, Baoshan District, Shanghai, China). Absorbance reading was performed on ChemWell 2910 branded ELISA reader device. (Awareness Technology, Inc. Martin Hwy. Palm City, USA). Results were reported in ng/ml.

Statistical analysis

The data were analyzed with the IBM SPSS® 25.0 (Armonk, NY, USA) package program. Continuous variables were controlled with the Shapiro-Wilks Test for distribution characteristics. Variables that fit to the Gaussian distribution characteristics were analyzed with parametric tests, whereas variables violating the normal distribution characteristics were analyzed with non-parametric tests. Difference analysis of numerical variables between groups was performed with Kruskal Wallis H Test.

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Mann-Whitney U Test (with Bonferroni correction) was used for the post-hoc analyzes. The relationship between continuous variables was analyzed by Pearson Correlation Analysis. In the correlation analysis, the power interpretation was made as follows: weak:0.0-0.24; medium: 0.25-0.49; strong: 0.50-0.74; very strong: 0.75-1.0 (18). Hepcidin markers were determined by linear regression analysis. Statistical differences were considered significant at the level of $p < 0.05$.

RESULTs

The study was completed with a total of 90 participants, including 30 patients with major depression, 30 patients with anxiety disorder, and 30 healthy volunteers. The clinical and sociodemographic data are presented in **Table 1**.

After the blood samples of the participants were collected, the frozen blood was thawed and the Hepcidin and Ferroportin levels were assessed (**Table 2**). When the groups were compared, Hepcidin levels in MDD patients were found to be significantly lower than in patients with an anxiety disorder (p=0.014). However, no statistically significant difference was observed between MDD and healthy controls or between anxiety disorder and healthy controls. It was determined that there was no difference between the groups in terms of Hepcidin and other iron metabolism parameters (serum Fe, total Fe binding, UIBC, ferritin). It was also determined that there was no difference in terms of complete blood count values and AST, ALP, LDH, bilirubin, direct bilirubin, indirect bilirubin, total protein levels, while a statistically significant difference was determined between ALT, GGT, and albumin levels.

It was observed that ALT and GGT levels in patients with anxiety disorder were significantly lower than in patients with major depression (ALT p= 0.011) (GGT p= 0.001). The albumin values, also known as negative phase reactants, showed that albumin levels in healthy controls were higher than in both major depression patients (p= 0.009) and anxiety disorder patients (p= 0.004).

In the correlation analysis, it was found that there was a weak inverse correlation between age and Hepcidin (r=-0.241), Ferroportin (r=-0.217), and albumin (r= -0.231). In terms of the clinical scales, there was a weak inverse (r=-0.240) correlation between the HAM-A and albumin, and a moderate inverse correlation (r=-0.289) between HAM-D and albumin. A moderate inverse correlation was observed between both two scales and ferritin levels. Also, an inverse correlation was observed between HAM-D and Ferroportin, but the strength of this correlation was weak (r= -0.214) (Table 3). According to the study data, the strongest correlation was found between Hepcidin and Ferroportin (r=0.635). A moderate linear correlation was observed between albumin and ferritin (r=0.292) and between ferritin and serum iron (r=0.398) (**Table 3**).

In the linear regression analysis, it was found that the predictors of Hepcidin level were direct bilirubin (B=-466.01, p=0.032) and MCV (B=4.91, p=0.039) in the MDD group, albumin (B=165.00, p=0.019) in the anxiety disorder group, and serum iron level in the healthy control group (B= -1.11, p= 0.026) (**Table 4**).

Table 1. Sociodemographic and clinical characteristics of all the groups

		MDD (%)	Anxiety Disorders n (%)	Healthy Controls n (%)	p
Age (mean±sd)		38.80±13.11	36.30±15.3	31.57±8.4	0.082
Gender	Female	25 (83.3)	23 (76.7)	13 (43.3)	
	Male	5 (16.7)	7 (23.3)	17 (56.7)	0.002*
Marital Status	Single/Divorced	7 (23.3)	10 (33.3)	19 (63.3)	
	Married	23 (76.7)	20 (66.7)	11 (36.7)	0.004*
Level of education	Uneducated	5 (16.7)	2 (6.7)	0	
	5 years of education	5 (16.7)	4 (13.3)	1 (3.3)	<0.001**
	8 years of education	10 (33.3)	5 (16.7)	0	
	12 years of education	4 (13.3)	11 (36.7)	5 (16.7)	
	University graduate	6 (20)	8 (26.7)	24 (80)	
Employment status	Employed	6 (20)	10 (33.3)	23 (76.7)	
	Unemployed/Retired	24 (80)	20 (66.7)	7 (23.3)	<0.001**
Smoking status	Smoker	9 (30)	7 (23.3)	13 (43.3)	
	Non-smoker	21 (70)	23 (76.7)	17 (56.7)	0.241
Suicide history	No	25 (83.3)	28 (93.3)	30 (100)	
	Yes	5 (16.7)	2 (6.7)	0	0.053
Illness duration (months) (mean±sd)		29.89±30.37	16.67±20.69	-	0.056
HAM-A (mean±sd)		15.53±4.95	22.20±8.42	2.73±3.43	<0.001** p†:0.002* p‡:<0.001** p¶:<0.001**
HDRS (mean±sd)		18.30±4.96	11.97±5.31	1.07±1.57	<0.001** p†:<0.001** p‡:<0.001** p¶:<0.001**

HAM-A: Hamilton Anxiety Rating Scale, HDRS: Hamilton Depression Rating Scale
*p<0.05
**p<0.001
p†: MDD- Anxiety disorders
p‡: MDD– Healthy controls
p¶: Anxiety disorders – Healthy controls

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Table 2. Comparisons between the groups in respect of biochemistry examinations

	MDD	Anxiety Disorders	Healthy Controls	p
Hepcidin med.(Q_1-Q_3)	147.4 (98.7-175.7)	188.9 (134.5-302.4)	172.6 (124.4-292.4)	0.038* p†: 0.014* p‡: 0.079 p¶: 0.425
Hepcidin mean±s.d	156±76.1	226.4±117.9	210.9±108.4	
Ferroportin med.(Q_1-Q_3)	6.4 (4.2-9.2)	7.8 (6.2-13)	8.8 (5-15.7)	0.135
Ferroportin mean ±s.d	7.7±4.7	10.5±6.0	10.6±6.9	
ALT med.(Q_1-Q_3)	16 (12-20)	12 (10-15)	15 (12-25)	0.016* p†: 0.011* p‡: 0.717 p¶: 0.015*
ALT mean±s.d	20.5±23.2	14.6±10.5	19.9±12.4	
AST med.(Q_1-Q_3)	19.5 (15-23)	17 (15-21)	18 (16-22)	0.353 p†: 0.211 p‡: 0.836 p¶:0.219
AST mean±s.d	20.3±9.2	17.8±5.3	18.9±4.4	
GGT med.(Q_1-Q_3)	16 (14-25)	11 (9-16)	17.5 (10-32)	0.007** p†: 0.001** p‡: 0.882 p¶: 0.057
GGT mean±s.d	21.2±12.7	13.9±8.4	21.9±15.2	
Albumin med.(Q_1-Q_3)	4.7 (4.6-4.9)	4.6 (4.5-4.8)	4.9 (4.7-5.1)	0.005** p†: 0.379 p‡: 0.009** p¶: 0.004**
Albumin mean±s.d	4.7±0.2	4.7±0.3	4.9±0.3	

*p<0.05
**p<0.01
p†: MDD- Anxiety disorders
p‡: MDD– Healthy controls
p¶: Anxiety disorders – Healthy controls
ALT: Alanine aminotransferase, AST:Aspartate aminotransferase, GGT:Gamma glutamyl transferase

Table 3. Correlation analysis between biochemical data and clinical data

Pearson Correlation		Age	HAM-A	HDRS	Hepcidin	Ferroportin	Albumin	Ferritin
HAM-A	r	-.017						
	p	.874						
HDRS	r	.184	.612**					
	p	.083	<.001					
Hepcidin	r	-.241*	-.045	-.199				
	p	.022	.673	.060				
Ferroportin	r	-.217*	-.029	-.214*	.635**			
	p	.040	.787	.043	<.001			
Albumin	r	-.231*	-.240*	-.289**	.143	.177		
	p	.029	.023	.006	.179	.095		
Ferritin	r	.015	-.273**	-.275**	-.104	-.105	.292**	
	p	.887	.009	.009	.328	.324	.005	
Total Iron	r	-.065	-.091	-.109	-.028	.042	.184	.398**
	p	.543	.394	.308	.790	.697	.082	<.001

*p<0.05 ** p<0.01
HAM-A: Hamilton Anxiety Rating Scale, HDRS: Hamilton Depression Rating Scale, Pearson Correlation Test

Table 4. Evaluation of Hepcidin levels in groups with regression analysis

		Unstandardized Coefficients B	Unstandardized Coefficients SE	Standardized Coefficients Beta	t	p
MDD	D. Bil	-466.01	205.80	-0.37	-2.26	0.032
	MCV	4.91	2.26	0.35	2.17	0.039
Anxiety Disorder	Albumin	165.00	66.29	0.43	2.49	0.019
Healthy Control	Serum Fe level	-1.11	0.47	-0.41	-2.36	0.026

D. Bil: Direct bilirubin, MCV: Mean corpuscular volume
Linear Regression Analysis (Stepwise). Dependent Variable: hepsidin, Independent variables: All clinical and biochemical variables. Depression Group: F=5.41, p=0.011, Adjusted R2=0.23; Anxiety Group: F=6.20, p=0.019, Adjusted R2=0.16; Healthy Control group: F=5.56, p=0.026, Adjusted R2=0.17.
SE: Standard Error

DISCUSSION

When the results were evaluated, it was determined that Hepcidin and Ferroportin levels were lower in the major depressive disorder group, and when compared to the anxiety group, Hepcidin levels were statistically significantly lower. In addition, when all participants were evaluated together, an inverse correlation was found between Ferroportin levels and the severity of depression. The regression analysis showed that the determinants of Hepcidin levels were direct bilirubin and MCV in the depression group. It was found that albumin levels in the anxiety disorder group and serum iron levels in the control group were negative determinants of Hepcidin levels.

Diet-related causes, vegetative symptoms of depression, neuroendocrine changes, inflammation, and oxidative stress may cause systemic metabolic effects in patients with MDD. The influence of nutrition and the biological systems of depression are highly related. In other words, nutrition can activate hormonal, neurotransmitter, and signaling pathways in the gut that modulate brain functions such as appetite, sleep, energy intake, neurogenesis, reward mechanisms, cognitive function, and mood (19). Exercise also has many known effects on metabolism. A study reported that Hepcidin levels increased after exercise, and iron metabolism was affected by exercise (20).

The relationship between sleep disorders and iron deficiency may also be involved (21). Therefore, symptoms such as sleep disturbance, appetite changes, and psychomotor retardation, which are expected to be seen in major depression, may be one of the factors affecting the metabolism of proteins that regulate iron metabolism. Besides, the effects of the drugs used are not yet known. A recent study found a relationship between chlorpromazine-equivalent doses of antipsychotic drugs and Ferroportin levels (22). These metabolic effects may have affected Hepcidin levels. The inverse relationship between the Ferroportin level and the severity of depression supports this view. Besides, Hepcidin is a protein that inhibits Ferroportin synthesis. The level of Hepcidin may also have decreased secondary to the low level of Ferroportin.

Some studies reported that Hepcidin levels were higher in Alzheimer's disease and attention deficit hyperactivity disorder (22, 23) and Ferroportin levels were lower in schizophrenia patients (24). These results provide evidence to iron turn over especially the Hepcidin - Ferroportin axis, may be impaired in psychiatric disorders.. This study is in line with this notion.

Age and gender are two crucial factors that affect iron metabolism. It is known that iron metabolism deteriorates with aging (25). Our study results show that age, Hepcidin, and Ferroportin levels are inversely correlated. However, in the gender evaluation, it was determined that there was no statistically significant difference in Hepcidin and Ferroportin levels. We inferred this result was due to the small sample size and gender distribution imbalance.

When the results were evaluated in aggregate, there was a difference between the depression group and the anxiety disorder group in terms of Hepcidin levels, while the healthy controls did not differ with both groups, which was attributed to the imbalance of gender distribution. As there is no significant difference in the sex ratios between the patient groups, the evaluations of this study between the patient groups are more valuable.

Limitations

The low number of samples, imbalance of gender distribution, and the study's cross-sectional nature are some of the limitations. Also, the fact that many of the patients included in the study were currently using antidepressants and that biomarkers have been studied from peripheral blood samples were limitations of our study. Without doubt, studies using CSF samples and imaging methods will help to enlighten the subject. Inflammation and vitamin D levels are shown to influence Hepcidin synthesis (26, 27). Future studies may analyze the interaction between inflammatory mechanisms and Hepcidin-Ferroportin levels.

CONCLUSION

The low levels of Hepcidin and Ferroportin both together in MDD indicate that the relationship between these two molecules is affected. Considering the long duration of the disease in the MDD group, it was thought that the treatment period was also prolonged and antidepressant use might have affected negative feedback. The inverse correlation between the severity of depression and Ferroportin is another important finding of this study. However, it is difficult to explain the causal relationship between depressive symptoms and Ferroportin. Large-scale follow-up studies on this subject will enlighten the subject. Experimental models may provide an opportunity to determine the secondary changes upon altered Hepcidin and Ferroportin levels.

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BKG, MIA: Revisions

Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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