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Investigating the Role of Oxidant-Antioxidant Balance in the Etiology of Migraine

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Abstract

Aim: Migraine, a prevalent neurovascular disorder, is marked by repetitive headache episodes. Its complex etiology encompasses biochemical, genetic, and environmental influences, but its exact pathophysiology remains elusive. Recent studies have hinted at a link between migraine and oxidative stress. Hence, this study sought to delve into the correlation between migraine, oxidative stress markers, and lipid profiles.

Material and Method: This case-control study involved 60 adult migraine patients from Dicle University's Neurology Department in Diyarbakır, Türkiye, observed between 2009 and 2010. The control group was age- and gender-matched healthy individuals. Parameters like malondialdehyde (MDA), paraoxonase-1 (PON-1), total antioxidant capacity (TAC), and lipid constituents such as total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were measured in both groups.

Results: Migraine sufferers, particularly those with aura, had significantly elevated MDA levels compared to controls ($p < 0.05$). Conversely, TAC and PON-1 levels were notably lower in the migraine population, suggesting an imbalance in their oxidant/antioxidant systems ($p < 0.05$). Lipid analysis showed heightened TC, LDL-C, and TG in migraine patients, while HDL-C was diminished, with marked differences in subgroups ($p < 0.05$).

Conclusion: The surge in MDA and the decline in TAC and PON-1 levels insinuate that oxidative stress plays a pivotal role in migraine's pathophysiology. The lipid profile alterations in migraineurs highlight potential cardiovascular concerns. Comprehensive cohort studies are essential to confirm these findings and understand the intricate ties between migraine, oxidative stress, and metabolic indicators. This research underscores oxidative balance's potential significance in migraine pathogenesis, emphasizing the need to consider oxidative stress in migraine management and prevention strategies.

Keywords: Migraine disorders, oxidative stress, malondialdehyde, arylidialkylphosphatase, lipids, cardiovascular diseases

INTRODUCTION

Migraine is a common neurovascular disease accompanied by several clinical features such as headache, nausea, and photophobia (1). Approximately 12%-16% of the general population, primarily women, suffers from migraine (2). Although many biochemical, genetic, and environmental factors have been suggested to play a role in the pathogenesis of migraine, the exact pathogenesis is still unclear (3-5). However, recent studies increasingly suggest that oxidative stress may play a central role in migraine's pathophysiology.

Oxidative stress refers to a shift in the antioxidant/oxidant balance in the direction of oxidants. Overproduction of reactive oxygen species causes damage to cells, organs,

and even the entire body (6). Malondialdehyde (MDA), the product of lipid peroxidation, has been used to assess oxidative status in various conditions, such as respiratory distress, cardiovascular problems, neuroinflammatory disorders, and cancer (7). Paraoxonase-1 (PON-1), a key antioxidant chemical, has anti-inflammatory and antiatherosclerotic characteristics, preventing low-density lipoprotein (LDL) and high-density lipoprotein (HDL) from oxidation (8-10). Total antioxidant capacity (TAC), an integrated parameter of detectable antioxidants, reflects the synergistic interaction of all antioxidants in serum or plasma (11).

Several studies have reported changes in oxidative stress marker levels in migraine patients, suggesting a possible relationship between oxidative damage and migraine. In a

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recent study, proteomics analysis revealed inflammatory and oxidative stress markers in the plasma of migraine patients during pain episodes, suggesting their use as potential disease biomarkers (12). Another study reported that botulinum toxin type-A (BoNT/A) treatment improved plasma oxidative stress biomarker levels, further confirming the role of oxidative stress in chronic migraine (13). Additionally, a study on the status of inflammatory and anti-inflammatory markers in migraine patients concluded that MDA, an oxidative stress marker, and other inflammatory markers may act as potential risk factors for migraine (14). On the other hand, other studies did not find any significant difference between migraine patients and healthy control subjects in oxidative stress marker levels (15-18). Hence, the exact nature of the complex relationship between oxidative stress and migraine remains unclear. Therefore, more comprehensive studies that will provide a deeper insight into the multifaceted role of oxidative stress in migraine are needed.

In this context, this study was carried out to comparatively assess the plasma levels of MDA, PON-1, TAC, and lipid profile in individuals with and without migraine with a view to clarifying the potential role of oxidant/antioxidant balance in migraine.

MATERIAL AND METHOD

Study Design and Ethical Considerations

This research was designed as a forward-looking, case-control study. Approval for the study protocol was obtained from the ethics committee of Dicle University, Diyarbakır, Türkiye, prior to initiation (Approval No: 14-26.05.12). The conduct of this study adhered to the ethical guidelines outlined in the Declaration of Helsinki. All participants provided their consent through signed, written informed consents.

Population and Sample

The research focused on adult individuals (over 18 years of age) diagnosed with migraine, monitored at the Dicle University, Diyarbakır, Türkiye's Faculty of Medicine, Neurology Department's outpatient clinic from 2009 to 2010. Migraine typically presents as repeated episodes of severe headaches that can last from 4 to 72 hours and are often exacerbated by everyday physical activities. Symptoms frequently accompanying migraines include nausea, vomiting, visual disturbances, and heightened sensitivity to light and sound (1). Migraine auras are characterized by reversible focal neurological symptoms involving visual, sensory, speech, and/or motor problems that develop gradually and usually precede the headache phase (19).

Consecutive patients between the ages of 20 and 50 who were diagnosed with migraine (with or without aura) by an experienced neurologist according to the International Classification of Headache Disorders version 3 Beta (ICHD-3 beta) criteria (1) had at least two migraine attacks per month, did not smoke or drink alcohol, were taking

regular medication in the last one month before the study at the minimum, and gave their consent to participate in the study were included in the study.

On the other hand, patients with major psychiatric or neurological disorders who had a history of pregnancy, breastfeeding, or menopause and have used any medication that may affect the levels of oxidant/antioxidant markers in the last month were excluded from the study.

In the end, 60 migraine patients who met the study inclusion criteria were included in the patient group (Group 1). Group 1 was divided into two subgroups: those with aura (Group 1a) (n=32) and those without aura (Group 1b) (n=28). The control group (Group 2) consisted of 30 age- and gender-matched healthy individuals with no personal or familial history of migraine or other headache disorders and who applied to the neurology outpatient clinic for other reasons during the study period.

Data Collection

Venous blood samples were taken to assess patients' serum MDA, PON-1, and TAC levels and lipid profiles. Blood samples were collected from all participants into heparinized tubes between 08:00 a.m. and 09:00 a.m. after fasting overnight. Blood samples were maintained in gel biochemistry tubes for 30 minutes, centrifuged at 3500 x g for 5 minutes to separate plasma, labeled, and promptly stored at -80°C until testing.

Lipid peroxidation was spectrophotometrically assessed in blood plasma using a 2-thiobarbituric acid-reactive substance (TBARS) assay (20) (Shimadzu UV-160, Cayman Chemical Company). MDA equivalents were used to calculate the TBARS levels. Tetramethoxypropane (TMP; 1, 1, 3, 3) was selected as the standard. The resulting data were presented in terms of $\mu\text{mol/L}$ plasma.

PON-1 enzyme activity was assessed using the Rel Assay Diagnostics PON enzyme test kit (Abbott Architect c16000 clinical chemistry analyzer). The activity of PON-1 towards paraoxon was measured spectrophotometrically at 412 nm (21). The enzyme activity in one micromole of p-nitrophenol produced in one minute was measured at 37°C using $17\ 100\ \text{M}^{-1}\ \text{cm}^{-1}$ as the molar extinction coefficient.

The plasma TAC level was assessed using the Rel Assay Diagnostics test kit and spectrophotometer (Abbott Architect c16000 clinical chemistry analyzer). The technique used for measuring plasma TAC levels employs a fully automated method, as formulated by Erel (22). His method is predicated on the discoloration of the typically more resilient 2,2'-azino-bis (3-ethylbenz-thiazoline-6-sulfonic acid) radical cation by antioxidants. The findings are expressed in terms of millimoles of Trolox equivalent per liter.

The study measured various biochemical parameters, namely total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol

(HDL-C), and triglycerides (TG). These assessments were conducted using established methods on an Abbott Architect c16000 clinical chemistry analyzer.

The study's primary and secondary outcomes were determined as migraine patients' oxidant/antioxidant levels and lipid profiles and the differences, if any, between migraine patients (with and without aura) and control subjects in oxidant/antioxidant levels and lipid profiles, respectively.

Statistical Analysis

The post-hoc power analysis revealed the statistical power of the independent two-sample t-test featuring the MDA values of Group 1a and the control group (Table 1) as 99%. In addition, the post-hoc power analysis revealed the statistical power of the independent two-sample t-test featuring the MDA values of Group 1b and the control group (Table 1) as 99%.

Given the sample size, these data suggest that our study featured adequate statistical power to detect the differences observed in MDA values between the migraine subgroups and the control group. The analysis was performed using the "statsmodels" library in Python (version 3.8.5).

For the analysis of our collected data, we utilized the SPSS 24.0 software suite (IBM Corp., Armonk, NY, U.S., 2016), a widely recognized tool for advanced statistical analysis. To ensure the robustness of our results, we first verified the normal distribution of our continuous data using the Kolmogorov-Smirnov test. This step is crucial as the normality of data can influence the choice of statistical tests and the validity of their outcomes.

Our continuous variables were then represented as

mean±standard deviation (SD) for clarity and ease of interpretation. In contrast, categorical variables were presented in terms of frequencies (n) and percentage (%) values, providing a comprehensive overview of the distribution of our data.

To compare categorical data, we employed Pearson's chi-square test, a standard method for understanding associations between categorical variables. We also utilized Levene's F-test to ensure the homogeneity of variances across our datasets.

Depending on the results of our preliminary tests and the nature of our data, we chose the most appropriate statistical tests for comparison. In the analysis of continuous variables, the study utilized either one-way analysis of variance (ANOVA) or the Kruskal-Wallis test, contingent upon the data distribution. ANOVA was applied for data that followed a normal distribution, whereas the Kruskal-Wallis test was used for data that did not. In cases of pairwise comparison, the selection between the student's t-test and the Mann-Whitney U test was also based on whether the data was normally distributed or not.

To validate the robustness of our results, each test was executed with a 95% confidence interval. A two-sided p-value of less than 0.05 was deemed indicative of statistical significance, aligning with the common benchmark in numerous scientific investigations.

RESULTS

Upon examining the baseline data, no notable disparities were observed in the anthropometric and demographic attributes across the groups. A detailed breakdown of the laboratory findings for each group can be referenced in Table 1.

Table 1. Laboratory data in all subjects by groups and subgroups								
Results*	Group 1 (Patient) (n=60)		Group 2 (Healthy control) (n=30)	p-values**				
	Group 1a (n=32)	Group 1b (n=28)		p1	p for ANOVA	p2	p3	p4
Oxidative and antioxidative parameters								
MDA	6.7±0.52	3.96±0.56	2.56±0.11	<0.001	<0.001	<0.001	<0.001	<0.001
PON-1	106.5±13.1	103.6±10.2	143.9±12.2	<0.001	<0.001	<0.001	<0.001	0.348
TAC	1.05±0.14	1.07±0.09	1.22±0.05	<0.001	<0.001	<0.001	<0.001	0.520
Lipid profile								
COL	-	-	-	<0.001	<0.001	>0.05	>0.05	0.007
HDL-C	40.2±9.4	49.9±9.2	40.6±7.8	<0.001	<0.001	0.856	<0.001	<0.001
LDL-C	114.7±15.5	98.0±13.1	85.1±26.0	<0.001	<0.001	<0.001	0.022	<0.001
TG	155.3±37.6	113.4±29.5	113.1±44.5	<0.001	<0.001	<0.001	0.976	<0.001

*Mean±SD values, **p-values are for One-way ANOVA or Kruskal Wallis in three group comparisons, P values are for Student t-test or Mann Whitney U test in two groups comparisons. p1: Group 1 and Group 2, p2: Group 1a and Group 2, p3: Group 1b and Group 2, p4: Group 1a and Group 1b. Group 1a: Migraine with aura, Migraine without aura, Group 2: Control, MDA: Malondialdehyde, PON-1: Paraoxonase-1, TAC: Total antioxidant capacity, COL: Total cholesterol, LDL-C: Low-density lipoprotein, HDL-C: High-density lipoprotein, TG: Triglyceride

When assessing oxidative stress markers, a pronounced increase in MDA levels was evident in both migraine subgroups when juxtaposed with the control group (Group 2) ($p < 0.05$). Conversely, antioxidant markers, specifically TAC and PON-1 levels, were discernibly diminished in migraine patients relative to the controls ($p < 0.05$). Delving into the lipid profiles, it was observed that TC, HDL-C, LDL-C, and TG concentrations were markedly elevated in patient groups (Group 1) compared to Group 2 ($p < 0.05$).

A deeper dive into the subgroups revealed that MDA concentrations were notably higher in the migraine patients with aura (Group 1a) than their counterparts without aura (Group 1b) ($p < 0.05$). However, no discernible differences were found between these subgroups

concerning TAC and PON-1 levels. In terms of lipid concentrations, the comparison of Group 1a and Group 1b revealed significantly higher TC, LDL-C, and TG levels in Group 1a ($p < 0.05$). While no significant disparity was found between Group 1a and the control group in terms of HDL-C levels ($p > 0.05$), Group 1b exhibited higher HDL-C levels when compared to both Group 1a and the control group ($p < 0.05$).

For a visual representation of the distribution of MDA, PON-1, and TAC levels across groups, please refer to Figure 1. Similarly, Figure 2 provides a graphical depiction of the distribution of TC, LDL-C, HDL-C, and TG levels among the groups.

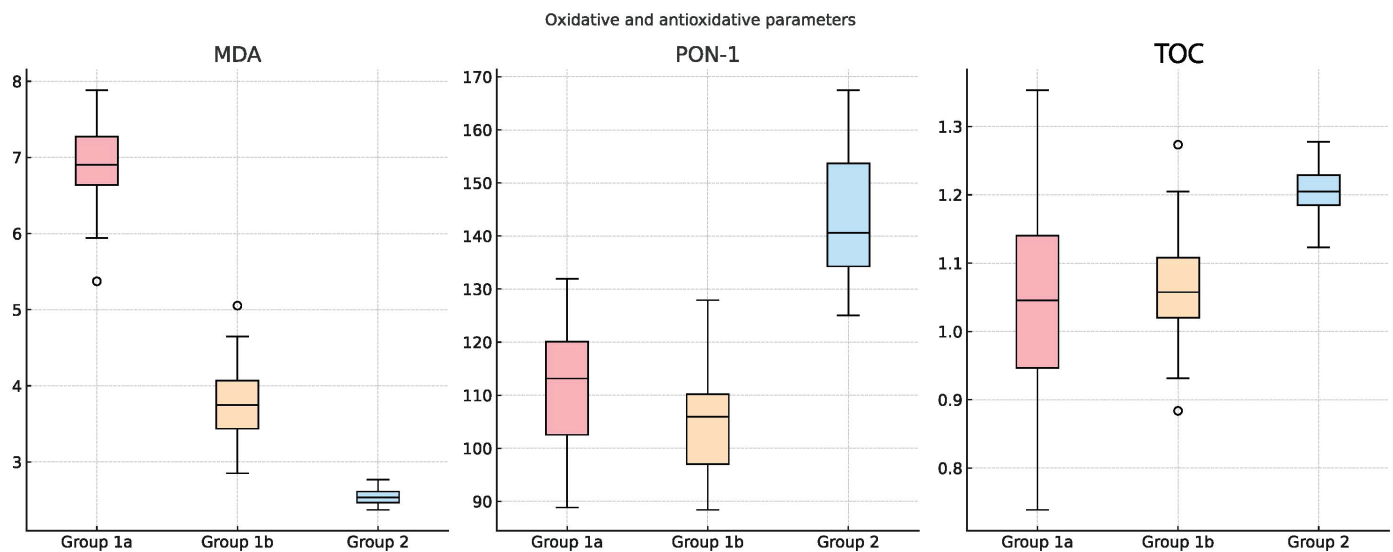


Figure 1. MDA, PON-1, and TAC levels across patient groups: Migraine with aura, migraine without aura, and control. MDA; malondialdehyde, PON-1; paraoxonase-1, TAC; total antioxidant capacity

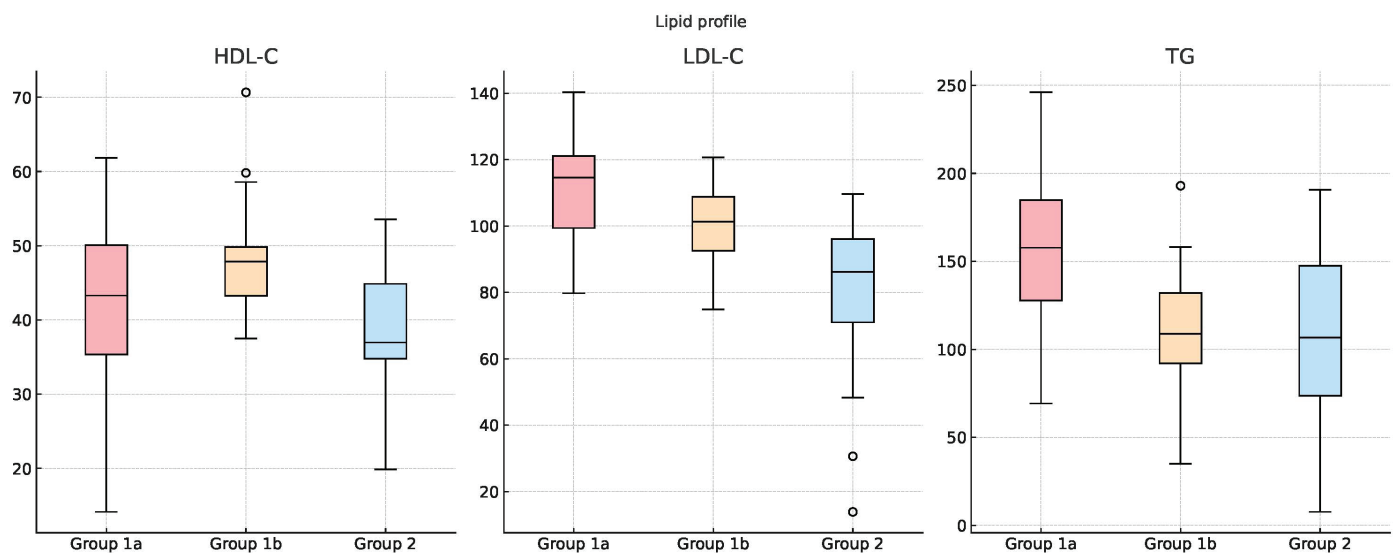


Figure 2. Analysis of the lipid profiles LDL-C, HDL-C, and TG levels among the patient groups: Migraine with aura, migraine without aura, and control. LDL-C; low-density lipoprotein, HDL-C; high-density lipoprotein, TG; triglyceride

DISCUSSION

The comparison of serum levels of specific metabolic markers, including MDA, PON-1, and TAC, between

migraine patients and healthy individuals revealed a significant increase in serum levels of oxidative stress markers, particularly MDA, in migraine patients, especially in those with aura. These findings were accompanied by

decreased antioxidant activity, as evidenced by reduced PON-1 and TAC levels.

There are numerous studies in the literature on oxidative stress markers in migraine. Dini et al. (13) reported that chronic migraine and medication overuse headaches were associated with a diminished antioxidant capacity, suggesting an imbalance in antioxidant processes in migraine patients. In parallel, in this study, the serum levels of oxidative and antioxidant stress markers, particularly MDA, were found to be significantly elevated in migraine patients than in healthy control subjects. In contrast, Bernecker et al. (23) did not find any significant difference in MDA levels between migraine patients and control subjects. Nevertheless, they reported increased levels of 4-hydroxy-2-nonenal (HNE), another lipid peroxidation biomarker.

PON plays a pivotal role in the plasma antioxidant system by providing protection against oxidative damage. Several studies, such as those by Yıldırım et al. (24) and Cakina et al. (25), reported significantly reduced PON activity in migraine patients compared to control subjects, whereas others, such as those by Eren et al. (18) did not find any significant difference in PON activity between migraine patients and control subjects. These discrepancies suggest the complexity of oxidative stress mechanisms in migraine.

Measurement of antioxidants individually can be challenging due to their interactive nature. Thus, TAC and the oxidative stress index (OSI) are often used to reflect the synergistic interaction of all antioxidants in serum or plasma. Eren et al. (18) did not observe significant differences in TAC and OSI levels between migraine patients and control subjects. On the other hand, Tripathi et al. reported decreased TAC levels in migraine patients after preventative therapy (26). Similarly, in our study, the TAC levels were significantly lower in both migraine subgroups compared to the control group.

Migraine has been associated with various cardiovascular risk factors, including lipid metabolic abnormalities. Kurth et al. (27) investigated the relationship between elevated lipid profile levels and cardiovascular diseases in a cohort of primarily non-reproductive aged women with migraines. They found that women with a history of migraine had a marginally increased risk of elevated TC and LDL-C levels. Similar findings have been reported in the literature (28-30). Tana et al. (28) observed a positive correlation between cholesterol levels and migraine severity and frequency. The study also suggested that migraine prophylaxis might reduce the levels of lipid parameters. Although the precise link between lipid profile and migraine severity has not been thoroughly documented, increased endothelial dysfunction, oxidative stress, and inflammation in migraine patients might contribute to an unfavorable lipid profile (28). Uygur-Kucukseymen et al. (30) found that migraine patients without aura had higher lipid levels, suggesting that migraine pathophysiology might be associated with elevated lipid levels. Moreover, different migraine characteristics, such as aura, were

unrelated to lipid metabolism. Consistent with these findings, our study observed significant changes in lipid profiles among migraine patients. We found significantly elevated levels of TC, LDL-C, HDL-C, and TG in migraine patients compared to healthy controls. The HDL-C levels in migraine patients without aura were augmented compared to those with aura, aligning with the findings of Uygur-Kucukseymen et al. (30). Additionally, TG levels were comparable between healthy controls and migraine patients without aura. Although, LDL-C levels are considered an indicator of cardiovascular risk in migraine patients with aura, conflicting findings in the literature warrant the need for further large-scale studies to clarify the subject.

Limitations of the Study

The relatively small sample size may be deemed the study's primary limitation, considering that it might have amplified the observed differences. Larger scale studies are needed to elucidate the differences between migraine subgroups further. In addition, the study's case-control design may be deemed another limitation of the study as it precluded establishing causality.

CONCLUSION

In conclusion, this study's findings indicated the significant elevations in serum levels of oxidative markers, particularly MDA, in migraine patients, particularly those with aura, and the concomitant decrease in the serum levels of antioxidant markers, PON-1 and TAC. These results suggest the potential role of oxidative balance in the pathophysiology of migraine, warranting further research to elucidate the implications of the changes in oxidative stress marker levels in migraine-related neuroinflammation.

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REFERENCES

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia Int J Headache. 2018;38:1-211.
2. Burch R, Rizzoli P, Loder E. The prevalence and impact of migraine and severe headache in the United States: Updated age, sex, and socioeconomic specific estimates from government health surveys. Headache J Head Face Pain. 2021;61:60-8.

3. Qubty W, Patniyot I. Migraine Pathophysiology. *Pediatr Neurol.* 2020;107:1-6.
4. Geyik S, Altunısık E, Neyal AM, Taysi S. Oxidative stress and DNA damage in patients with migraine. *J Headache Pain.* 2016;17:10.
5. Dong X, Guan X, Chen K, et al. Abnormal mitochondrial dynamics and impaired mitochondrial biogenesis in trigeminal ganglion neurons in a rat model of migraine. *Neurosci Lett.* 2017;636:127-33.
6. Varadhan S, Venkatachalam R, Perumal SM, Ayyamkulamkara SS. Evaluation of oxidative stress parameters and antioxidant status in coronary artery disease patients. *Arch Razi Inst.* 2022;77:853-9.
7. Tsikas D, Mikuteit M. N-Acetyl-L-cysteine in human rheumatoid arthritis and its effects on nitric oxide (NO) and malondialdehyde (MDA): analytical and clinical considerations. *Amino Acids.* 2022;54:1251-60.
8. Godbole C, Thaker S, Salagre S, et al. A prospective study to assess the role of paraoxonase 1 genotype and phenotype on the lipid-lowering and antioxidant activity of statins. *Indian J Pharmacol.* 2023;55:179-84.
9. Mehvari F, Imanparast F, Mohaghegh P, et al. Protective effects of paraoxonase-1, vitamin E and selenium, and oxidative stress index on the susceptibility of low density lipoprotein to oxidation in diabetic patients with/without coronary artery disease. *Eur J Med Res.* 2023;28:300. Erratum in: *Eur J Med Res.* 2023;28:459.
10. Nasreen FJ, Balasubramaniam G. Paraoxonase gene polymorphisms: understanding the biochemical and genetic basis of coronary artery disease. *J Taibah Univ Med Sci.* 2023;18:257-64.
11. Rico D, Cano AB, Álvarez Álvarez S, et al. Study of the total antioxidant capacity (TAC) in native cereal-pulse flours and the influence of the baking process on TAC using a combined bayesian and support vector machine modeling approach. *Foods.* 2023;12:3208.
12. Togha M, Rahimi P, Farajzadeh A, et al. Proteomics analysis revealed the presence of inflammatory and oxidative stress markers in the plasma of migraine patients during the pain period. *Brain Res.* 2022;1797:148100.
13. Dini E, Mazzucchi S, De Luca C, et al. Plasma levels of oxidative stress markers, before and after BoNT/A treatment, in chronic migraine. *Toxins.* 2019;11:608.
14. Bhoi S, Nanda R, Dash S, et al. Status of inflammatory and anti-inflammatory parameters in migraine: a case-control study. *Int J Med Rev Case Rep.* 2022;6:33-6.
15. İçme F, Erel O, Avci A, et al. The role of oxidative stress markers in the pathophysiology of migraine and after treatment. *Neurosurg Q.* 2014;24:286-90.
16. Yang Z, Xu P, Geng C, Zhang H. Evaluation of simple antioxidant blood parameters in patients with migraine. *Front Neurol.* 2022;13:939363.
17. Togha M, Razeghi Jahromi S, Ghorbani Z, et al. An investigation of oxidant/antioxidant balance in patients with migraine: a case-control study. *BMC Neurol.* 2019;19:323.
18. Eren Y, Dirik EB, Neşelioğlu S, Erel Ö. Serum lipid profiles, relationship between paraoxonase/arylesterase activity and high-density lipoprotein levels in patients with migraine. *Turk J Neurol.* 2017;23:117-21.
19. Lai J, Dilli E. Migraine aura: updates in pathophysiology and management. *Curr Neurol Neurosci Rep.* 2020;20:17.
20. Zhao M, Li Y, Bai X, Feng J, Xia X, Li F. Inhibitory effect of guava leaf polyphenols on advanced glycation end products of frozen chicken meatballs (-18°C) and its mechanism analysis. *Foods.* 2022;11:2509.
21. Adkins S, Gan KN, Mody M, La Du BN. Molecular basis for the polymorphic forms of human serum paraoxonase/arylesterase: glutamine or arginine at position 191, for the respective A or B allozymes. *Am J Hum Genet.* 1993;52:598-608.
22. Erel O. A novel automated direct measurement method for total antioxidant capacity using a new generation, more stable ABTS radical cation. *Clin Biochem.* 2004;37:277-85.
23. Bernecker C, Ragginer C, Fauler G, et al. Oxidative stress is associated with migraine and migraine-related metabolic risk in females. *Eur J Neurol.* 2011;18:1233-9.
24. Yıldırım S, Akar S, Kuyucu M, et al. Paraoxonase 1 gene polymorphisms, paraoxonase/arylesterase activities and oxidized low-density lipoprotein levels in patients with migraine. *Cell Biochem Funct.* 2011;29:549-54.
25. Çakina S, Yücel S, Polat CÇ, Öztürk Ş. Oxidative stress parameters in patients with migraine without aura. *Namık Kemal Tıp Derg.* 2020;8:31-5.
26. Tripathi GM, Kalita J, Misra UK. A study of oxidative stress in migraine with special reference to prophylactic therapy. *Int J Neurosci.* 2018;128:318-24.
27. Kurth T, Gaziano JM, Cook NR, et al. Migraine and Risk of Cardiovascular Disease in Women. *JAMA.* 2006;296:283. Erratum in: *JAMA.* 2006 Aug 9;296(6):654. Erratum in: *JAMA.* 2006;296:1 p following 291.
28. Tana C, Santilli F, Martelletti P, et al. Correlation between migraine severity and cholesterol levels. *Pain Pract.* 2015;15:662-70.
29. Maghbooli M, Jameshorani M, Afshar S, Kamali K. The prevalence of metabolic syndrome parameters and their association with headache characteristics among migraineurs. *Curr J Neurol.* 2021;20:190-201.
30. Uygur-Kucukseymen E, Akca G. Serum lipid profile in migraine and its association with clinical characteristics. *Neurol Res.* 2023;45:57-61.



Long Term Comparison of Hamstring Tendon Autograft and Tibialis Anterior Tendon Allograft Use in ACL Reconstruction

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Abstract

Aim: In the early 2000s, the optimal graft for anterior cruciate ligament (ACL) reconstruction was a subject of uncertainty. Today, autografts have become the gold standard in this procedure. Aim of this study is to contribute to the existing knowledge by conducting a comprehensive comparison of the long-term clinical outcomes between hamstring allografts and anterior tibialis tendon allografts (ATT) in the context of ACL reconstruction.

Material and Method: This study was conducted based on individuals who were operated on with the diagnosis of symptomatic ACL rupture 10 years ago. Participants were randomly assigned to undergo ACL reconstruction using either hamstring autografts or anterior tibialis allografts. All allografts were procured from a single tissue bank, underwent aseptic processing, and were fresh-frozen without terminal irradiation. Patient assessments included questionnaires based on the Lysholm knee scoring scale (LKSS) and the International Knee Documentation Committee (IKDC) subjective knee score. Objective functional tests, such as the Lachman test and pivot-shift, were performed, accompanied by a comprehensive physical examination of the knee.

Results: A total of 60 patients, comprising 58 males and 2 females, with a mean age of 29.48 ± 6.2 , were included in the study. Predominant symptoms reported were pain and giving-way phenomena. Significantly different LKSS values were observed between the preoperative and postoperative periods for both anterior tibialis allograft and hamstring autograft patients ($p < 0.001$). Similarly, a significant difference was noted in the preoperative and postoperative IKDC scores for all patients ($p < 0.001$).

Conclusion: Based on our research findings, both the hamstring autograft and allograft methods demonstrate success in improving LKSS and IKDC scores for patients undergoing ACL repair surgery. Notably, the autograft group exhibits a more pronounced improvement compared to the allograft group.

Keywords: Lysholm knee scoring scale, International Knee Documentation Committee score, autograft, allograft, anterior cruciate ligament reconstruction

INTRODUCTION

Anterior cruciate ligament (ACL) ruptures account for 50% of all knee joint ligament injuries. The incidence of ACL ruptures ranges between 25-78 per 100,000 individuals, with approximately 70% of these injuries attributed to sports-related activities (1-3).

Despite advancements in early detection and effective treatment options, ACL injuries persist as a significant health concern, impacting mobility and daily activities (4-6). Surgical intervention is recommended for active young athletes with specific conditions, including meniscal lesions, unstable knee joints, combined ligament injuries, and persistent pain unresponsive to non-surgical

therapies (7-9). The primary objective of reconstruction is to stabilize the knee, eliminating movement restrictions within the joint. Failure to undergo reconstruction may lead to an increased risk of degenerative arthritis (10).

Various surgical techniques have been proposed in the realm of ACL injury repair. While multiple methods, including primary or supportive sutures, exist for ligament repair, anatomical reconstruction with grafting stands out as the preferred and well-established approach (11-13).

The existing literature predominantly addresses three primary grafting techniques: allograft, autograft, and synthetic grafts. Notably, synthetic grafts are infrequently utilized due to documented negative clinical and

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surgical outcomes (6,9,11-13). Autografts commonly utilized include those sourced from the patellar tendon, hamstring tendon, and quadriceps tendon. On the other hand, allografts undergo a series of procedures, including freezing, drying, and irradiation of the patellar tendon or tibialis anterior tendon from the donor (6).

The utilization of soft tissue grafts in ACL surgery has experienced a surge, primarily attributable to advancements in femoral and tibial fixation methods. Notably, the hamstring tendon autograft has gained popularity owing to its comparable clinical outcomes, reduced discomfort during kneeling, less anterior knee pain, diminished donor site morbidity, and a lower likelihood of injuring the extensor mechanism (14-18).

Over the past decade, there has been an increased prevalence of allograft usage in both primary and revision ACL surgery. In a study conducted by Maletis et al., allografts were employed in 42.4% of primary and 78.8% of revision ACL reconstructions, based on a community-based registry encompassing over 16,000 ACL reconstructions (19). The principal advantage of allograft tissue lies in the absence of donor site morbidity. Additional benefits include a quicker recovery period, improved aesthetics, a range of graft types and sizes, and overall reduced costs (20-23). However, allogenic tissue does pose certain risks, such as the potential for disease transmission, delayed integration, and decreased graft stiffness and strength depending on the processing method utilized with higher cost (24-26).

This study compares the long-term clinical results of anterior tibialis tendon (ATT) allografts and hamstring allografts in the setting of ACL restoration in order to advance existing knowledge.

MATERIAL AND METHOD

A cross-sectional retrospective study was conducted, involving participants diagnosed with symptomatic ACL insufficiency who underwent primary ACL reconstruction between 2008 and 2010. The study included patients who had not undergone prior surgery on the affected knee, possessed a minimum follow-up duration of 12 months, and were skeletally mature. Exclusion criteria encompassed patients with multiple ligament injuries or chondral lesions graded higher than grade 2 (Outerbridge grade 3,4) (27).

After receiving the approval of the Ethics Committee (no:E2-23-4869 date: 09/08/2023) the participants were categorized into two groups based on the type of graft used: hamstring autograft and tibialis anterior allograft. Allografts for all patients were provided by the same licensed tissue bank. These allografts underwent aseptic harvesting, were freshly frozen, and did not undergo terminal irradiation.

Operative Technique

All procedures were performed under spinal anesthesia. Patients were positioned in a supine manner on the

operating table, with the knee flexed over the end of the table. The application of a pneumatic tourniquet was standard. In the Hamstring group, a longitudinal incision was made over the pes-anserinus. The semitendinosus and gracilis tendons were harvested using a closed-loop tendon stripper, and any residual muscle tissues covering the excised graft were meticulously cleansed. In the tibialis anterior group, allografts were rehydrated for 30 minutes in warm saline. The free ends were prepared using the Krakow method with Ethibond (No. 5).

Arthroscopic ACL reconstruction was performed using a trans-tibial approach. Partial meniscectomies were performed when required, graft-femoral fixation was conducted using endobutton and this approach was applied to both the hamstring autograft and tibialis anterior allograft groups. Subsequently, the knee was positioned in full extension, and the graft was securely held while a helper executed an anterior drawer technique. The graft was then anchored in place using a bioabsorbable interference screw. Additional support to the fixation was provided by the use of a ligament staple (28).

Rehabilitation

On the day of surgery, patients were equipped with an angle-adjustable knee brace, and movement during the initial postoperative week was restricted by locking the brace at 0 degrees of extension. Beginning on the first postoperative day, all patients underwent mobilization, with efforts made to push their tolerance to the extent of pain. The angle settings of the knee braces were gradually modified to facilitate 30, 60, and 90 degrees of flexion in the first, second, and third weeks, respectively. Sutures were removed from all patients during the second week, and they were uniformly referred to the same physical therapy facility to commence the rehabilitation process.

Patient Evaluation

Patients were followed for an average of 11.2 ± 1.6 years following the original procedure, and results were assessed and contrasted. The functional outcomes of the patients were evaluated using the Lysholm knee scoring scale (LKSS) and the International Knee Documentation Committee (IKDC) evaluation form. To conduct these assessments, patients' complaints and activity levels were examined at both the preoperative and final controls. A comparison of the results from preoperative and postoperative control physical examinations enabled the analysis of joint range of motion, Lachman tests, anterior drawer tests, the presence of pain at the graft extraction site, as well as surgical wound morbidity and the risk of disease transmission (29,30).

Statistical Analysis

The conformity of the data to the normal distribution was tested with the Shapiro-Wilks test. The Wilcoxon test was performed because the dependent group comparisons did not distribute the data normally. Independent group comparisons were made using the t-test if the data were normally distributed, and the Mann-Whitney test if the

data were not normally distributed. The pre-post operation changes between the groups were compared by taking the difference score. Descriptive statistics were given as mean±standard deviation in case of using parametric tests, and as median (min-max) value in case of non-parametric tests. Categorical data were compared with Chi-square or Fisher's exact tests. Categorical data were given as frequency and percentage. The relationships between the variables were analyzed using the Pearson correlation coefficient in case the data showed normal distribution and the Spearman correlation coefficient in the opposite case. Significance level of 0.05 or less was taken as statistical significance level. SPSS v.25 package program was used in the analysis of the data.

RESULTS

Eighty patients with ACL ruptures visited our facility once in a month and were followed remotely for an average of 11.2±1.6 years following the original procedure. Twenty patients, however, were eliminated from the study for various reasons: six refused to take part, seven were lost to follow-up, four had cartilage lesions at the time of surgery that were graded higher than II by the Outerbridge classification, two had PCL injuries, and one had a collateral ligament injury. The study included 60 patients in total—58 men and 2 women—retrospectively. Of these, thirty patients had ATT allografts used for ACL reconstruction, and the other thirty patients had hamstring autografts used for the same purpose. All patients in both groups underwent postoperative evaluations. At the time of injury, the mean age was 29.48±6.2, and the distribution of this age was similar in the allograft (30.13±5.41) and autograft (28.83±6.39) groups. Table 1 provides a summary of the homogeneity observed in the two groups. Regarding age, the LKSS, the Lachman test, the pivot-shift test, pain, and knee damage in preoperative values, no statistically significant differences were observed between the groups. However, there was a statistically significant difference between the groups as indicated by the IKDC and loosening preoperative values. The allograft group exhibited higher IKDC and loosening values in comparison to the autograft group.

Table 1. Homogeneity comparisons between groups

n (%)	Allograft (n=30)	Autograft (n=30)	p-value
Age	30.13±5.41	28.83±6.39	0.398
LKSS preop	65 (58:72)	65 (57:72)	0.888
IKDC preop	80 (70:85)	63.5 (54:71)	<0.001
Lachman test	19 (63.3)	23 (76.7)	0.260
Pivot shift test	15 (50)	9 (30)	0.114
Additional knee damage	10 (33.3)	14 (46.7)	0.292
Pain	7 (23.3)	7 (23.3)	1.000
Loosening	9 (30.0)	2 (6.7)	0.020

LKSS: lysholm knee scoring scale, IKDC: International Knee Documentation Committee

Table 2 shows the preoperative and postoperative IKDC and LKSS compressions. In both groups postoperative results of IKDC and LKSS scores were significantly better than preoperative results.

Table 2. Pre-post comparison within groups

		n	Median (Min:Max)	
Allograft group	LKSSpreop	30	65 (58:72)	<0.001
	LKSSpostop	30	94 (64:98)	
	IKDCpreop	30	80 (70:85)	0.004
	IKDCpostop	30	83 (70:89)	
Autograft group	LKSSpreop	30	65 (57:72)	<0.001
	LKSSpostop	30	96 (68:98)	
	IKDCpreop	30	63.5 (54:71)	<0.001

LKSS: lysholm knee scoring scale, IKDC: International Knee Documentation Committee

The analysis of the change in values from preoperative to postoperative in both the allograft and autograft groups yields a statistically significant difference in the scores obtained from the IKDC and the LKSS. In particular, during the switch from preoperative to postoperative exams, the LKSS and IKDC scores of the autograft group increased noticeably more than those of the allograft group (Table 3).

Table 3. Change of values in LKSS and IKDC scores between groups

	Allograft (n=30)	Autograft (n=30)	p-value
LKSS change value	26 (3:38)	30.5 (5:41)	0.006
IKDC change value	3.97±6.64	13.4±6.92	<0.001

LKSS: lysholm knee scoring scale, IKDC: International Knee Documentation Committee

Notable conclusions are drawn when comparing the scores between the two groups on the IKDC and LKSS depending on the existence of additional preoperative and postoperative injuries. (Table 4). IKDC scores in the allograft group showed a statistically significant difference among individuals who did not have additional knee injury. Similarly, preoperative and postoperative LKSS scores in the allograft group exhibited a statistically significant difference in patients with additional knee injury, with an increase observed in postoperative values compared to preoperative levels. Conversely, there was no statistically significant difference in preoperative and postoperative IKDC scores in patients with additional knee damage in the allograft group. In the autograft group, a statistically significant change was noted in preoperative and postoperative LKSS ratings among patients without additional knee injury. Postoperative values showed an increase compared to preoperative levels.

Table 4. Pre-post comparison of LKSS and IKDC scores within groups according to additional knee injury				n	Median (Min:Max)	p-value
Allograft group	Additional knee injury (-)	preop	LKSS	20	64.5 (58:72)	<0.001
		postop	LKSS	20	94.5 (64:98)	
		preop	IKDC	20	74 (70:85)	
		postop	IKDC	20	83 (70:89)	
	Additional Knee Injury (+)	preop	LKSS	10	65.5 (63:70)	0.005
		postop	LKSS	10	93 (69:97)	
		preop	IKDC	10	82 (70:85)	
		postop	IKDC	10	83 (70:87)	
Autograft group	Additional knee injury (-)	preop	LKSS	16	65.5 (57:72)	<0.001
		postop	LKSS	16	96 (68:98)	
		preop	IKDC	16	63.5 (55:68)	
		postop	IKDC	16	76 (66:84)	
	Additional knee injury (+)	preop	LKSS	14	64 (59:71)	0.001
		postop	LKSS	14	96 (69:98)	
		preop	IKDC	14	63 (54:71)	
		postop	IKDC	14	78.5 (65:82)	

LKSS: lysholm knee scoring scale, IKDC: International Knee Documentation Committee

Based on the change values within the allograft and autograft groups, the comparison of preoperative to postoperative LKSS and IKDC scores was examined, taking into account the existence or nonexistence of additional knee damage. The change in values between

the groups is summarized in Table 5.

There was an statistically increase in IKDC and LKSS scores in all groups except IKDC scores in allograft group with pain(Table 6).

Table 5. Intergroup comparisons of LKSS and IKDC change of values according to additional knee injury status						
		n	Allograft	n	Autograft	p-value
Additional knee injury (-)	LKSS change value	20	26 (4:38)	16	28 (8:41)	0.149
	IKDC change value	20	6 (-13:17)	16	13 (-2:25)	0.002
Additional knee injury (+)	LKSS change value	10	26 (3:31)	14	33 (5:38)	0.005
	IKDC change value	10	1.7±4.06	14	14.36±7.66	<0.001

LKSS: lysholm knee scoring scale, IKDC: International Knee Documentation Committee

Table 6. Preoperative-postoperative comparison within groups according to pain condition					
		n	Median (Min:Max)	p-value	
Allograft Group	Pain (-)	LKSSpreop	23	65 (58:70)	<0.001
		LKSSpostop	23	95 (64:97)	
		IKDCpreop	23	75 (70:85)	
		IKDCpostop	23	82 (70:89)	
	Pain (+)	LKSSpreop	7	65 (63:72)	0.018
		LKSSpostop	7	92 (67:98)	
		IKDCpreop	7	82 (71:84)	
		IKDCpostop	7	84 (70:87)	
Autograft Group	Pain (-)	LKSSpreop	23	65 (59:72)	<0.001
		LKSSpostop	23	96 (69:98)	
		IKDCpreop	23	63 (54:71)	
		IKDCpostop	23	77 (65:84)	
	Pain (+)	LKSSpreop	7	65 (57:71)	0.018
		LKSSpostop	7	95 (68:98)	
		IKDCpreop	7	64 (55:68)	
		IKDCpostop	7	70 (66:82)	

LKSS: lysholm knee scoring scale, IKDC: International Knee Documentation Committee

A statistically significant increase was noted in the autograft group among individuals who did not experience pain when comparing the change values of the LKSS and IKDC scores between the groups based on the presence

of pain. Nonetheless, when it came to people who were in pain, there was no discernible difference between the two groups (Table 7).

Table 7. Intergroup comparisons of LKSS and IKDC change according to pain status

		n	Allograft	n	Autograft	p-value
Pain (-)	LKSS change value	23	27 (3:38)	23	31 (5:38)	0.017
	IKDC change value	23	4.48±6.12	23	13.96±6.01	<0.001
Pain (+)	LKSS change value	7	24 (4:31)	7	27 (8:41)	0.209
	IKDC change value	7	3 (-13:13)	7	13 (-2:25)	0.097

LKSS: lysholm knee scoring scale, IKDC: International Knee Documentation Committee

There were no documented cases of reoperations or significant complications. Furthermore, there were no cases of infection, arthrofibrosis, or deep vein thrombosis reported in the study.

DISCUSSION

Restoring the knee to its pre-injury state is the main goal of ACL reconstruction surgery. A key factor in accomplishing this objective is the selection of the graft; a good graft should have characteristics like no morbidity at the donor site, accessibility, strength for quick healing, and instant incorporation. Our study's objective was to look into the long-term clinical results of two popular soft tissue grafts for ACL restoration in a patient population that was comparable to our own. We focused on making the graft type the only dependent variable in the research. We used the same surgical technique, femoral and tibial fixation techniques, and postoperative rehabilitation regimen for every patient in order to maintain uniformity.

Due to its advantageous characteristics, such as comparable clinical outcomes, decreased anterior knee pain and discomfort when kneeling, lower donor site morbidity, and a lower risk of potential extensor mechanism injuries, the hamstring tendon autograft has become more and more common in ACL surgery (14,16,17,22,28). Allografts, which have additional benefits like a quicker recovery time, better aesthetics, a range of graft sizes, and lower overall costs, were utilized more frequently in the 2000s for both primary and revision ACL surgery (20–23,29,30). Nevertheless, there are issues with allogenic tissue, such as the possibility of disease transmission, delayed integration, and, depending on how it is processed, decreased stiffness and strength of the graft (24, 25). Contradictory findings have been found when comparing the clinical outcomes of autografts and allografts. While some case series report no appreciable differences, others point to a higher failure rate (31,32).

The usefulness of hamstring autografting and anterior tibialis tendon allografting for ACL reconstruction was compared in this study. We utilized established metrics that are frequently used in the literature to assess the results, such as the IKDC evaluation form and the LKSS. We also looked at how preoperative pain and the existence of extra knee pathologies affected these scores. Using this method, we were able to thoroughly evaluate and compare

the functional results of the two grafting techniques while taking into account significant factors like pain and related knee conditions. However, it was noted that in terms of subjective scores, hamstring autograft fared better than anterior tibialis allograft.

Previous research comparing hamstring autograft and allograft techniques in ACL reconstruction has been examined in the literature. Yang et al. (33) discovered that both methods produced comparable long-term results (mean one year) in a cohort design trial with 175 patients, even though the allograft group showed more laxity and immunologic response in the early postoperative period. With the exception of irradiated allografts, which performed similarly to autografts, another study by Grassi et al. in a meta-analysis on revision ACL reconstruction showed that autografts had better outcomes with lower laxity and complication rates than allografts (34). LKSS and IKDC values in our study significantly improved in both graft groups when compared to baseline. Interestingly, when comparing the change levels, the autograft group's improvement was more significant. More specifically, LKSS increased by 30.5 in the autograft group and by 26 in the allograft group. In terms of IKDC scores, there was a mean increase of 13.4 in the autograft group and 3.97 in the allograft group. In contrast, no differences were observed in side-to-side laxity, Lysholm, IKDC, or Tegner activity ratings at the final examination with a minimum 3-year follow-up in a study by Edgar et al. that randomly assigned 104 patients to receive either a hamstring autograft or hamstring allograft (35). The results of our study showed improvements in both groups' LKSS and IKDC scores; however, the autograft group's change in values was more noticeable than the allograft group's. We conclude that autografts outperformed allografts in patients without preoperative knee pain. There was no appreciable difference between the groups when it came to pain. Autografts performed better than allografts in patients with additional knee injuries, such as osteoarthritis and ligament damage. Notably, in terms of knee stability and clinical outcomes, Riccardo D'Ambrosi et al. found no clinical difference between autograft and allograft (36).

Every patient in our study randomly assigned to the allograft group received a fresh-frozen tibialis anterior

tendon allograft from the same tissue bank. Reduced donor site hypoesthesia, enhanced cosmetics, the capacity to procure grafts of any size needed, and a reduction in stiffness in the surgical knee are just a few benefits that come with using allografts (37). The fact that there were no cases of disease transmission linked to the use of allografts in our investigation is comforting.

In a young, active group, Bottoni et al. (38) found that the use of an allograft rather than an autograft for initial ACL restoration resulted in a graft failure rate that was more than three times higher. In a similar vein, Sun et al. allocated 208 patients at random to receive a fresh-frozen hamstring allograft or an autograft of the hamstring. Despite some knees exhibiting laxity on the KT-2000 arthrometer, they did not find any overt graft failures or the need for revision in their study, which included a mean follow-up of 7.8 years (39). A different study conducted by Edgar et al. with a minimum 3-year follow-up period discovered no variation in anteroposterior laxity at the final examination (40). No graft failures were noted during the course of our investigation, which included a 13-year follow-up period. The absence of graft failures in our study could be attributed to various factors, including the exclusion of young athletes who could overstretch their grafts, the patients' sedentary lifestyles, or the patients' discontinuation of the activities that caused their ACL damage in the first place. These factors might be responsible for the good outcomes and long-term stability observed in our patient group.

There are a few significant issues with this study. The generalizability and depth of the study's conclusions may be impacted by the lack of information regarding the etiologic causes of ACL rupture and the interval between the injury and surgery. Furthermore, a small study population and a retrospective design introduce potential biases that could limit the findings' generalizability.

In order to improve the robustness and generalizability of the findings, future research could take into account addressing these limitations by implementing a prospective design, offering comprehensive details on the genesis and timing of ACL ruptures, and enlarging the study population.

In summary, this study showed that both hamstring autograft and anterior tibialis allograft produced positive long-term (10 years) clinical outcomes for ACL restoration. According to the results, the clinical outcomes, anteroposterior laxity, and failure rates of autograft and allograft are similar. It was observed, nevertheless, that hamstring autograft outperformed anterior tibialis allograft in terms of subjective scores.

CONCLUSION

It is imperative to recognize that the aforementioned conclusions are predicated upon the data at hand and the particular attributes of the population under investigation. More research with bigger and more varied patient groups is advised for a more thorough and reliable comparison.

By taking these factors into account, we can gain a better understanding of the relative effectiveness and results of various graft types used in ACL reconstruction.

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REFERENCES

1. Yasen SK, Borton ZM, Eyre-Brook AI, et al. Clinical outcomes of anatomic, all-inside, anterior cruciate ligament (ACL) reconstruction. *The Knee*. 2017;24:55-62.
2. Nordenvall R, Bahmanyar S, Adami J et al. A population-based nationwide study of cruciate ligament injury in Sweden, 2001-2009: incidence, treatment, and sex differences. *Am J Sports Med*. 2012;40:1808-13.
3. Doğan Ö, Çalışkan E, Gencer B. Clinical results of single bundle anterior cruciate ligament reconstruction with hamstring autograft. *Akdeniz Tıp Dergisi*. 2019;5:504-9.
4. Karakoç Y, Özanel E. Comparison of hamstring tendon autograft and tibialis anterior allograft methods in anterior cruciate ligament reconstruction surgery: a retrospective study. *Acta Oncologica Turcica*. 2021;54:103-10.
5. Burnham JM, Wright V. Update on anterior cruciate ligament rupture and care in the female athlete. *Clin Sports Med*. 2017;36:703-15.
6. Davies GJ, McCarty E, Provencher M, Manske RC. ACL return to sport guidelines and criteria. *Curr Rev Musculoskelet Med*. 2017;10:307-14.
7. Vundelinckx B, Herman B, Getgood A, Litchfield R. Surgical indications and technique for anterior cruciate ligament reconstruction combined with lateral extra-articular tenodesis or anterolateral ligament reconstruction. *Clin Sports Med*. 2017;36:135-53.
8. Karakoç Y, Atalay İB. The role of magnetic resonance imaging and clinical assessments in predicting meniscal tear surgery. *Eklemler Hastalıkları Cerrahisi*. 2019;30:85-90.
9. Muller B, Hofbauer M, Wongcharoenwatana J, Fu FH. Indications and contraindications for double-bundle ACL reconstruction. *International orthopaedics*. 2013;37:239-46.
10. Nordenvall R, Bahmanyar S, Adami J, et al. Cruciate ligament reconstruction and risk of knee osteoarthritis: the association between cruciate ligament injury and post-traumatic osteoarthritis. a population based nationwide study in Sweden, 1987–2009. *PLoS One*. 2014;9:e104681.
11. Atik OŞ. Autografts or allografts for anterior cruciate ligament reconstruction?. *Eklemler Hastalıkları Cerrahisi*. 2013;24:125.
12. Demirağ B, Ermutlu C, Aydemir F, Durak K. A comparison of clinical outcome of augmentation and standard reconstruction techniques for partial anterior cruciate ligament tears. *Eklemler Hastalıkları Cerrahisi*. 2012;23:140-4.

13. Pujol N, Colombet P, Cucurulo T, et al. Natural history of partial anterior cruciate ligament tears: a systematic literature review. *Orthop Traumatol Surg Res.* 2012;98:S160-4.
14. Ahldén M, Kartus J, Ejerhed L, et al. Knee laxity measurements after anterior cruciate ligament reconstruction, using either bone–patellar–tendon–bone or hamstring tendon autografts, with special emphasis on comparison over time. *Knee Surg Sports Traumatol Arthrosc.* 2009;17:1117-24.
15. Biau DJ, Tournoux C, Katsahian S, et al. Bone-patellar tendon-bone autografts versus hamstring autografts for reconstruction of anterior cruciate ligament: meta-analysis. *BMJ.* 2006;332:995-1001.
16. Forster MC, Forster IW. Patellar tendon or four-strand hamstring? A systematic review of autografts for anterior cruciate ligament reconstruction. *Knee.* 2005;12:225-30.
17. Goldblatt JP, Fitzsimmons SE, Balk E, Richmond JC. Reconstruction of the anterior cruciate ligament: meta-analysis of patellar tendon versus hamstring tendon autograft. *Arthroscopy.* 2005;21:791-803.
18. Wagner M, Kääh MJ, Schallock J, et al. Hamstring tendon versus patellar tendon anterior cruciate ligament reconstruction using biodegradable interference fit fixation: a prospective matched-group analysis. *Am J Sports Med.* 2005;33:1327-36.
19. Maletis GB, Inacio MC, Funahashi TT. Analysis of 16,192 anterior cruciate ligament reconstructions from a community-based registry. *Am J Sports Med.* 2013;41:2090-8.
20. Caborn DN, Selby JB. Allograft anterior tibialis tendon with bioabsorbable interference screw fixation in anterior cruciate ligament reconstruction. *Arthroscopy.* 2002;18:102-5.
21. Cole DW, Ginn TA, Chen GJ, et al. Cost comparison of anterior cruciate ligament reconstruction: autograft versus allograft. *Arthroscopy.* 2005;21:786-90.
22. Pearsall AW 4th, Hollis JM, Russell GV Jr, Scheer Z. A biomechanical comparison of three lower extremity tendons for ligamentous reconstruction about the knee. *Arthroscopy.* 2003;19:1091-6.
23. Sherman OH, Banffy MB. Anterior cruciate ligament reconstruction: which graft is best? *Arthroscopy.* 2004;20:974-80.
24. Arnoczky SP. The biology of allograft incorporation. *J Knee Surg.* 2006;19:207-14.
25. Eagan MJ, McAllister DR. Biology of allograft incorporation. *Clin Sports Med.* 2009;28:203-14.
26. Genuario JW, Faucett SC, Boublik M, Schlegel TF. A cost-effectiveness analysis comparing 3 anterior cruciate ligament graft types: bone-patellar tendon-bone autograft, hamstring autograft, and allograft. *Am J Sports Med.* 2012;40:307-14.
27. Liu Y, Liu X, Liu Y, Yang S. Comparison of clinical outcomes of using the nonirradiated and irradiated allograft for anterior cruciate ligament (ACL) reconstruction: A systematic review update and meta-analysis. *Medicine (Baltimore).* 2022;101:e29990.
28. Chen L, Cooley V, Rosenberg T. ACL reconstruction with hamstring tendon. *Orthop Clin North Am.* 2003;34:9-18.
29. Tegner Y, Lysholm J. Rating systems in the evaluation of knee ligament injuries. *Clin Orthop Relat Res.* 1985:43-9.
30. Höher J, Münster A, Klein J, et al. Validation and application of a subjective knee questionnaire. *Knee Surg Sports Traumatol Arthrosc.* 1995;3:26-33.



Downregulation of miR-568 in Atrial Fibrillation Leads to Increased Expression of NAPMT and TRMP7

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Abstract

Aim: Atrial fibrillation (AF) is known as the most common permanent cardiac arrhythmia worldwide with its incidence and prevalence gradually increase with age and cause significant morbidity and mortality. However, the epigenetic alterations underlying the development of this disease remains less understood. MicroRNAs (miRNAs), as one of the epigenetic regulators, are small non-coding RNAs that can target multiple genes to modulate proteins in different signaling pathways. Current studies have demonstrated that miRNAs, which are pivotal regulators of gene expression, may be involved in the pathophysiology of AF. The current study aims to clarify the miRNA regulated cellular signaling in atrial fibrillation.

Material and Method: An AF model was generated by providing external electrical stimulation to the HL-1 mouse cardiomyocyte cell line for 24 hours in this study. To understand the molecular mechanisms of miRNAs underlying the AF model, miRNA microarray analysis was performed. The gene sets obtained from the microarray analysis and the bioinformatically obtained putative targets were intersected and pathway enrichment analysis was performed. qRT-PCR was performed for validation of the selected miRNAs and potential targets.

Results: miRNA expression profile changes between the control group without external stimulation and the samples at the end of 3-, 6-, 12- and 24-hour stimulation were compared with microarray analysis. In particular, our transcriptomic analysis showed 5 distinctively expressed miRNAs (DEmiRNAs) whose target genes are associated with cardiovascular development within the stimulated groups in HL-1 cells. Additionally, our bioinformatics analysis revealed that targets of these miRNAs are concentrated in biological processes associated with cardiovascular development: smooth muscle cell proliferation, muscle cell proliferation, cell morphogenesis involved in differentiation and regulation of cell differentiation. Specifically, qPCR-based analyses confirmed the inverse correlation of miR-568 and potential targets of this miRNA. While miR-568 expression decreased with prolonged stimulation, expression of its potential targets, NAMPT and TRPM7, increased during prolonged stimulation.

Conclusion: This study supported the potential regulative role of miRNAs and their targets in the development of AF.

Keywords: Atrial fibrillation, miR-568, NAMPT, TRPM7

INTRODUCTION

Atrial fibrillation (AF) is known as the most common arrhythmia in the clinic, occurring with uncoordinated atrial contractions as a result of irregularities in atrial activation (1,2). AF is linked to atrial remodeling of the left atrium (3), and it is unclear whether AF is the ultimate consequence of atrial remodeling caused by heart disease combined with harmful environmental factors or is the main cause of progressive remodeling. AF and its complications are accountable for significant morbidity and mortality in adults. Like other cardiac arrhythmias, physiological approaches have been tried to be developed to explain

the etiology of AF, but over time it has been seen to have a complex pathogenesis and molecular approaches have begun to be developed in the last two decades. Although the electrophysiological and molecular changes occurring in cardiac tissue have been described by studies, the molecular mechanism needs to be elucidated in more detail in order to develop therapeutic strategies for AF (4).

From a pathophysiological standpoint, AF is primarily characterized by atrial electrical remodeling involving ion channel alterations (5), as well as structural remodeling (fibrosis and apoptosis) that supports the recurrence and persistence of arrhythmias (6). Atrial arrhythmogenic

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remodeling, characterized by changes in atrial structure or function that facilitate atrial arrhythmias, is a fundamental aspect of AF. This remodeling can stem from pre-existing cardiac conditions, systemic influences or factors like aging or the presence of AF itself. Recent studies have underscored the significance of remodeling in AF, offering new insights into fundamental mechanisms, and novel biomarkers are being developed to monitor remodeling processes based on these findings. Notably, the importance of abnormalities in intracellular Ca²⁺ processing has been emphasized, both for inducing ectopic activity and activating Ca²⁺-related cell signaling that drives profibrillator remodeling. Furthermore, the involvement of microRNAs (miRNAs), a recently identified category of small noncoding RNA sequences that control gene expression, has become apparent in both electrical and structural remodeling.

Recent investigations have unveiled the significant role of miRNAs in the onset and progression of cardiovascular disease (7). miRNAs, a group of small non-coding RNAs with high conservation, oversee nearly all cellular processes by exerting post-transcriptional control. They achieve this by binding to complementary sequences within the 3'-UTR region of target mRNAs, subsequently instigating the degradation or inhibition of translation for these mRNAs (8,9).

Given that these small RNAs can modulate multiple target mRNAs and that several miRNAs can target candidate mRNAs, the dysregulation of miRNAs is understandably a hallmark of many pathological conditions. miRNAs are employed as disease biomarkers due to their tissue- and pathology-specific expression. The functional miRNAs have been offered as potential targets for diverse cardiac conditions and arrhythmogenesis (10-12). It is crucial to establish direct cause-and-effect relationships between miRNAs and their mRNA targets to comprehend the molecular mechanisms driving diseases and to formulate precise therapeutic interventions. Increasing evidence indicates that miRNAs regulate processes such as modulation of Ca²⁺ handling, controlling cardiac excitability and cardiac conduction (13,14).

The stability and detectability of miRNAs in biofluids, including peripheral blood, position them as promising diagnostic biomarkers for various cardiovascular diseases. However, further investigations are required to assess circulating miRNAs as dependable biomarkers for AF. Studies centered on miRNAs hold considerable value in comprehending the mechanisms driving AF, evaluating miRNAs' potential roles as biomarkers, and advancing miRNA-based therapies.

The HL-1 cell line, derived from cardiac muscle, exhibits a gene expression pattern resembling that of typical mice atrial cardiomyocytes. In addition to preserving their capacity to divide without reverting to an embryonic state, HL-1 cells preserve cardiac morphology properties, electrophysiological characteristics and biochemical attributes (15). In this study, we appraised

the transcriptomic profile of miRNAs and relation with potential gene targets in AF using the HL-1 cells.

MATERIAL AND METHOD

Cell Culture and Generation of AF Model

The HL-1 cell line was purchased from Sigma-Aldrich (Cat. No: SCC065, St. Louis, Missouri, USA), and cells were cultured in Claycomb medium (Sigma, 51800C) supplemented with 10% fetal bovine serum (FBS) (Sigma, F7524, St. Louis, Missouri, USA), 1% penicillin/streptomycin (Sigma, P4333, St. Louis, Missouri, USA), 0.1 mM Norepinephrine (Sigma, A0937, St. Louis, Missouri, USA), and 2 mM L-Glutamine (Sigma, G7513, St. Louis, Missouri, USA). Flasks were coated with 3 mL of gelatin (Sigma, G9391, St. Louis, Missouri, USA)/fibronectin (Roche, 10838039001, Basel, Switzerland) for 1 hour in a humidified atmosphere at 37°C and 5% CO₂.

For the AF model, cells were seeded into 6-well plates, and using the carbon electrode IonOptix C-Dish™ integrated with the IonOptix C-Pace EP Cell Culture Stimulator 100 pacer system, a 5 Hz for 4 s (P1 wave) and 1 Hz for 1 s at 1.5V/cm³ current per well (P2 wave) was applied to the cells. HL-1 cells, seeded at 1x10⁶ per well in 6-well plates, were stimulated for 3, 6, 12, and 24 hours. Electrical capture in the stimulated cells was confirmed using microscopy, and the data are provided in Figure 1.

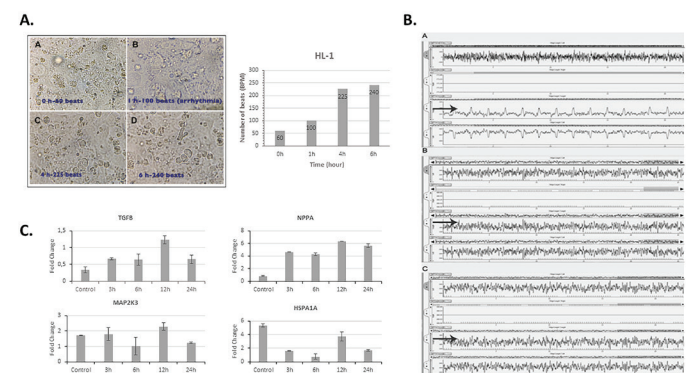


Figure 1. Supportive information of our AF model, **1A.** Microscope images of HL-1 cells as a result of electrical stimulation and change in the number of pulses made by HL-1 cells depending on the time of electrical stimulation, **1B.** Electrocardiogram images of cells stimulated in AF modeling. (a) represents control group, (b) represents 3rd hour and (c) represents 6th hour. **1C.** The onset of transcriptomic changes in response to stimulation were analysed in qRT-PCR ($p < 0.05$)

RNA Isolation

Briefly, cells were homogenized using Qiazol reagent (Qiagen, 79306, Hilden, Germany), and chloroform (Sigma, C2432, St. Louis, Missouri, USA) was added and vigorously mixed. The samples were then incubated at room temperature for 2 minutes and centrifuged at 13,300 rpm for 15 minutes at 4°C. After collecting the supernatant aqueous phase into a fresh tube, isopropanol (Sigma, I9516, St. Louis, Missouri, USA) was added, and the mixture was centrifuged again at 13,300 rpm for 15 minutes at 4°C. Subsequently, the samples were washed twice with 70% ethanol. The RNA integrity of the samples was then assessed.

Transcriptome Analysis

The analysis of miRNA expression was performed on total RNA extracted from cells in the unstimulated control group, with samples taken at four different stimulation times (3rd, 6th, 12th, and 24th hours). Microarray procedures were carried out according to the Affymetrix Whole Transcript (WT) Expression Arrays instruction manual. Briefly, 250 ng of total RNA extracted from cells was labeled with the Whole Transcriptome Reagent Kit (ThermoScientific, P/N 902280, Massachusetts, USA). The labeled samples were then purified and hybridized with the Mouse Gene 2.0 array (ThermoScientific, Massachusetts, USA). Arrays were scanned on the Affymetrix Scanner 7G, and image analysis was performed using Expression Console™ Software v1.4 (ThermoScientific, Massachusetts, USA), followed by data normalization and analysis using BRB-ArrayTools.

Quantitation of miRNA and mRNAs

Total RNA was isolated using Qiazol reagent (Qiagen, 79306, Hilden, Germany). For the detection of miRNA expression, 1 µg of RNA was converted to cDNA with the Mir-X miRNA First-Strand Synthesis Kit (Takara, 638313, Kusatsu, Shiga, Japan). The TB Green Advantage® qPCR Premix was then employed along with specific primer sets for mmu-miR-568. RNU6 was used as an internal reference for analysis.

To detect mRNA expression, cDNA was generated from 1 µg total RNA using the First Strand cDNA Synthesis Kit (Roche, 11483188001, Basel, Switzerland). GAPDH was employed for coding gene normalization. qRT-PCR was performed using the LightCycler® 480 Real-Time System (Roche, Basel, Switzerland). Primers for miR-568 and coding genes are provided in Table 1.

Table 1. Sequences of primers for GAPDH, PIK3CA, NAMPT, TRPM7, RBM20, miR-568 and RNU6

Gene ID	Sequences (5'to 3')	Amplicon (bp)
PIK3CA	F: ACGACCATCTTCGGGTGAAC	131 bp
	R: GTTTGATGGTGACGAGTGTGG	
GAPDH	F: TGTGTCCGTCGTGGATCTGA	150 bp
	R: TTGCTGTTGAAGTCGCAGGAG	
NAMPT	F: CCACCGACTCGTACAAGGTT	131 bp
	R: TGTTTCCTCGTATTTACCTTCCT	
TRPM7	F: TCTGTGGTCGTTTGGTCAAGCA	140 bp
	R: TGTTGGGCTCTGCTCCGTG	
RBM20	F: AGAGATGCCTGCGTTATGCC	139 bp
	R: GGAGCTTGGCAGCATTGTTGG	
mmu-miR-568	F: GTGGGGGATGTATAAATGTAT	-
	R: CTCGCTTCGGCAGCACA	
RNU6	F: CTCGCTTCGGCAGCACA	-
	R: AACGCTTCACGAATTTGCGT	

Bioinformatic Analysis

Screening DE miRNAs

Differentially expressed miRNAs (DE miRNAs) were screened using the Excel-based software package BRB-ArrayTools. This tool aids in identifying DE miRNAs between groups of samples and controls. In the present study, DE miRNAs between four different stimulation times and the unstimulated control group were selected based on statistical significance ($p < 0.05$ and $|\log_{2}FC| > 0.5$).

The clustering of the DE miRNAs and visualization of the clustering via heatmap was also performed by BRB-ArrayTools.

Target prediction analysis

To identify predictive targets for miR-568, MiRWalk was utilized. Additionally, TargetScan was employed to identify the 3'UTR binding sites of the miR-568-targeted genes. The list of AF-related genes was obtained from NCBI-Gene (<https://www.ncbi.nlm.nih.gov/gene>).

Statistical Analysis

Statistical significance was determined using Student's

t-test (p value of < 0.05) and the data are presented as the mean+SD.

RESULTS

AF Model Confirmation

To assess the AF pattern in the HL-1 cell line, electrical stimulations were observed for 24 hours under specific current and conditions. As a control, the number of pulses was measured before subjecting HL-1 cells to electrical stimulation, revealing a consistent rate of 60 pulses per minute (bpm). No change in the beat frequency was observed during the initial 30 minutes. However, starting from the 1st hour, the cells exhibited an increase in beats to 100 bpm, and irregularities in beat rhythm became apparent. Subsequently, the number of beats reached 105 bpm after 90 minutes, approximately 225 bpm at the end of the 4th hour, and around 240 bpm at the end of the 6th hour, as documented in microscope records (Figure 1A). This value aligns with the occurrence of arrhythmic beats (approximately 300 bpm) observed in atrial fibrillation patients.

To evaluate the potential development of an AF model

following electrical stimulation applied to HL-1 cells, electrocardiogram images were recorded using IonOptix Myocyte Calcium Photometry and Contractility Systems (Figure 1B). According to the obtained records, regular waves were observed in the control group cells that were not stimulated, while irregularities were detected in the cell pulse waves in the 3rd and 6th hour samples of stimulation.

In addition to electrocardiogram analysis, qRT-PCR analysis was performed using *HSPA1A*, *TGFB*, *NPPA*, and *MAP2K3* genes, whose expression profiles are reported to change in atrial fibrillation in the literature. As illustrated in Figure 1C, significant changes were detected as early as 3 hours after the initiation of rapid stimulation. The onset of transcriptomic changes in response to stimulation suggests the establishment of the AF pattern in these cells.

Analysis of DE miRNA in HL-1 Cells

Among the differentially expressed miRNAs in response to each stimulation time, (3h, 12h and 24 h) 5 miRNAs were found to be common, which were miR-568, miR-let7c-1, miR-145a, miR-490 and miR-505 (Figure 2A). Based on the heatmap analysis, miR-568, let-7c-1, and miR-145a exhibited increased level of expression during the initial 3 hours of stimulation. Subsequently, their expression levels gradually declined in a time-dependent manner, extending from 3 hours to 24 hours (Figure 2B). We also confirmed the decreasing expression pattern of miR-568 by qRT-PCR in control and 24 h stimulated cells (Figure 2C). It may also important to note that the mature sequence of miR-568 was found to be evolutionary conserved between human, mouse and rat (Figure 3).

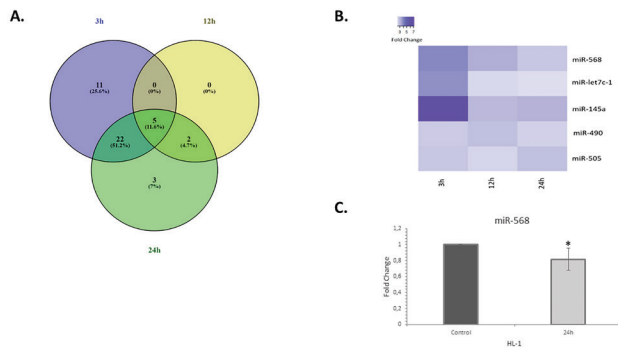


Figure 2. DE miRNA screening, **2A.** According to intersection analysis of samples with different stimulation time, 5 common differential expressed miRNAs was shown, **2B.** The heatmap graph containing the varying expression values of the 5 common microRNAs. **2C.** Down-regulation of miR-568 was confirmed by RT-PCR (n=3, *p<0.01)

miR-568 Sequences

Human	gaa <u>u</u> aacacua <u>u</u> auuu <u>AUGUAUAAAUGUAUACACAC</u> Cuuccuauauguaccacauauauauagu
Mouse	acacua <u>u</u> auuu <u>AUGUAUAAAUGUAUACACAC</u> Cuuccuauauauguccacauauauaugcgugugugugu
Rat	gua <u>u</u> acacua <u>u</u> auuu <u>AUGUAUAAAUGUAUACACAC</u> Cuuccuauauguccacacauauauacagugu

Figure 3. miR-568 mature sequence conserved between human, mouse and rat. Multiple sequence alignment of the section of quasi-alignment for the species showing perfect alignment and sequences which is labeled blue one is mature form of miRNA

To elucidate the role of miR-568 in HL-1, we gathered its target genes using various databases, such as miranda, miRDB, miRWalk, and Targetscan. A total of 428 targets

were identified and their enrichment in biological processes was assessed using Gene Ontology analysis. Among the GO analysis results, our emphasis was on the significant processes associated with cardiovascular development, such as the regulation of smooth muscle cell proliferation (FDR=0.022013, p value=0.0000040424) and muscle cell proliferation (FDR=0.034534, p value=0.0000082563), cell morphogenesis involved in differentiation (FDR=0.0010253, p value=3.1379e-8), and regulation of cell differentiation (FDR=0.0013541, p value=7.4599e-8).

Pathway enrichment analysis was performed to delve into the molecular functions of the targets associated with miR-568 by using KEGG. The enrichment analysis of identified gene targets for miR-568 revealed involvement in various KEGG pathways, notably the cAMP signaling (FDR=0.030316, p value=0.000095936), mTOR signaling (FDR=0.023211, p value=0.000073219), FoxO signaling (FDR=0.00013671, p value=4.2064e-7) and Rap1 signaling (FDR=0.037255, p value=0.00011903).

miR-568 Enhances the Expression of AF-Related Genes in HL-1 Cells

To demonstrate the potential role of miR-568 in AF, we intersected the targets of miR-568 with the AF-related gene list and found 4 genes (*NAMPT*, *TRPM7*, *RBM20* and *PIK3CA*) in common (Figure 4A). qRT-PCR results showed that the expression of AF-related genes, including *NAMPT* and *TRPM7* were significantly increased in 4 different stimulation times in a time dependent manner. Meanwhile, expression of *RBM20* and *PIK3CA* were markedly decreased in stimulation groups (Figure 4B). The converse expression patterns of miR-568 and its targets *NAMPT* and *TRPM7* at the same time points supported the potential role of them in AF and led us to identify the interaction between these miRNA and target genes.

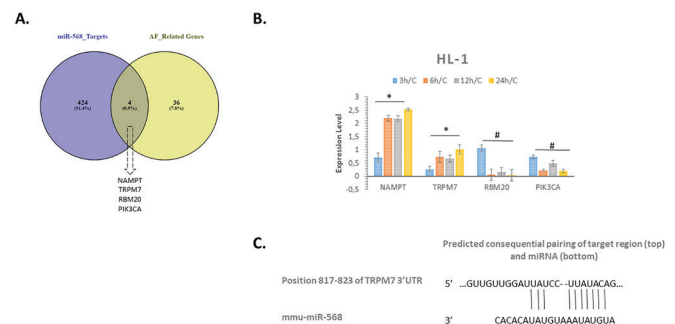


Figure 4. TRPM7 is a target gene of miR-568, **4A.** Identification of *NAMPT*, *TRPM7*, *RBM20* and *PIK3CA* as a common target of miR-568, **4B.** qRT-PCR was performed to determine the expression levels of predicted target genes of miR-568 in HL-1 cells, **4C.** Predicted mmu-miR-568 (MI0005517) seed match to the sequence in the 3'UTR of *TRPM7* mRNA. The seed sequences of miR-568 are AAU AUGU

miR-568 Interacts with 3-UTR of TRPM7 Gene

Analysis of the TargetScan showed that *TRPM7* was a potential target gene of miR-568. The matching positions for miR-568 within 3'-UTR of the targeted *TRPM7* mRNA are shown in Figure 4C.

DISCUSSION

AF is the most common clinical arrhythmia and by 2060 it is anticipated to attain a prevalence of 18 million in Europe (16). Patients with atrial fibrillation experience higher mortality rates and current therapeutic options do not fully address the clinical need for AF. Exploring the cellular mechanisms behind AF and devising innovative strategies to enhance the survival of individuals with AF are promising avenues for future research.

Over the past decade, substantial strides have been made in understanding AF and its underlying mechanisms, leading to the identification of numerous genetic (17-19) and epigenetic factors (20,21). In this context, miRNAs have recently been included among the molecular factors linked to the progression of AF, particularly in electrical and structural remodeling, that represent the two primary elements of atrial remodeling caused by fibrosis (22,23). Associations between cardiovascular diseases and miRNAs have been accelerated in recent years. A number of miRNAs have been described to be differently expressed and to modulate signaling pathways during cardiovascular diseases. It has been showed that miR-208 could act as a therapeutic molecule in cardiac fibrosis, heart failure and myocardial hypertrophy (24). Collectively, miR-595 and miR-155 exhibited a positive correlation with the left ventricular mass (LVM) index, while miR-182, miR-200a, and miR-568 demonstrated a negative correlation with the LVM index (25).

miR-568 was one of the differentially expressed miRNAs in response to stimulation in our study and its downregulation through increased stimulation times was confirmed by qRT-PCR. Meanwhile its putative targets, TRPM7 and NAMPT showed increased expression patterns which is expected since the miRNA-target expression patterns are inversely correlated. These findings may support the potential role miR-568 together with its targets TRPM7 and NAMPT in the development of AF. Among TRP channels, TRPM7 is particularly abundant in heart tissue (26,27) and is highly expressed myocardium during embryonic stage (28). Intercellular ICa transitions are greatly altered in atrial myocytes during AF. The reshaped regulation of calcium within cells is a significant factor in the emergence of impaired contractile function and alterations in atrial electrophysiology, specifically the remodeling of both contractile and electrical aspects, which are distinctive features of AF. TRPM7 current has recently been observed to undergo upregulation in atrial fibrillation. It is suggested that TRPM7 may serve as a calcium entry pathway, triggering TGF- β 1 signaling, thereby contributing to the development of atrial pathogenesis (29). NAMPT exhibits high expression in cardiomyocytes, and recent studies have demonstrated its impact on various cardiac conditions such as dilated cardiomyopathy, ischemia/reperfusion injury, and heart failure (30-32). However, there is a lack of reports on the correlation between AF and Nampt. Given the association of the Nampt/NAD axis with obesity and aging, crucial risk factors for AF, it is postulated that the Nampt/NAD axis plays a significant

role in the pathogenesis of obesity-related AF (33). The RNA-binding motif protein 20 (RBM20) gene, serves as a splicing factor (34) and is notably expressed in striated muscles, particularly the heart, and has been shown to significantly impact the splicing patterns of key genes essential for cardiac function (35,36). The manifestation of RBM20 cardiomyopathy is marked by a deeply penetrating and aggressive nature, closely linked to sudden cardiac death arrhythmias and heart failure (37,38). More than 30 genes have now been shown to be targets of RBM20. This encompasses additional genes vital for sarcomeric function, along with numerous genes essential for the efficient utilization of calcium in cardiomyocytes (39).

The complexity of the arrhythmia known as AF encompasses its genetic bases and inheritability. Significant advancements have been made in various areas, including risk assessment for AF, the discovery of new therapeutic targets, and the development of prediction models based on the genome. It is evident that gaining a deeper insight into the molecular mechanism of AF will not only enhance prediction models for the condition but will also pave the way for more effective personalized treatment approaches.

In this study, we generated an AF model in HL-1 cells through a directed electrical stimulation protocol that predominantly exhibits atrial-like electrophysiologic properties. This work involves characterizing and interrogating the genome-wide profiling of miRNA expression in atrial fibrillation. miR-568 expression was downregulated in HL-1 cells. Using bioinformatics approaches, we demonstrated a potential relation of miR-568 with cardiovascular development and related signaling pathways. miRNAs, including down-regulated miR-568, miR-let-7c-1, and miR-145a, as well as certain genes, including *NAMPT*, *TRPM7*, *RBM20*, and *PIK3CA*, might be related to a greater risk of AF.

CONCLUSION

It could be concluded that miR-568 may involve in the AF development or the impact of AF through regulating its putative targets *NAMPT* and *TRPM7*. Given that the mature sequence of miR-568 is conserved in humans, it would be valuable to confirm these data in human samples with further studies.

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REFERENCES

1. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace*. 2016;18:1609-78.

2. Lau DH, Linz D, Sanders P. New findings in atrial fibrillation mechanisms. *Card Electrophysiol Clin.* 2019;11:563-71.
3. Nattel S, Harada M. Atrial remodeling and atrial fibrillation: recent advances and translational perspectives. *J Am Coll Cardiol.* 2014;63:2335-45.
4. Saljic A, Heijman J, Dobrev D. Emerging antiarrhythmic drugs for atrial fibrillation. *Int J Mol Sci.* 2022;23:4096.
5. Brundel BJ, Van Gelder IC, Henning RH, et al. Alterations in potassium channel gene expression in atria of patients with persistent and paroxysmal atrial fibrillation: differential regulation of protein and mRNA levels for K⁺ channels. *J Am Coll Cardiol.* 2001;37:926-32.
6. Santulli G, D'Ascia C. Atrial remodeling in echocardiographic super-responders to cardiac resynchronization therapy. *Heart.* 2012;98:517; author reply 517.
7. Nattel S, Heijman J, Zhou L, Dobrev D. Molecular basis of atrial fibrillation pathophysiology and therapy: a translational perspective. *Circ Res.* 2020;127:51-72.
8. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell.* 2004;116:281-97.
9. Filipowicz W, Bhattacharyya SN, Sonenberg N. Mechanisms of post-transcriptional regulation by microRNAs: are the answers in sight?. *Nat Rev Genet.* 2008;9:102-14.
10. Tijssen AJ, Creemers EE, Moerland PD, et al. MiR423-5p as a circulating biomarker for heart failure. *Circ Res.* 2010;106:1035-9.
11. Fichtlscherer S, De Rosa S, Fox H, et al. Circulating microRNAs in patients with coronary artery disease. *Circ Res.* 2010;107:677-84.
12. D'Alessandra Y, Devanna P, Limana F, et al. Circulating microRNAs are new and sensitive biomarkers of myocardial infarction. *Eur Heart J.* 2010;31:2765-73.
13. Grueter CE, van Rooij E, Johnson BA, et al. A cardiac microRNA governs systemic energy homeostasis by regulation of MED13. *Cell.* 2012;149:671-83.
14. Latronico MVG, Condorelli G. MicroRNA-dependent control of the cardiac fibroblast secretome. *Circ Res.* 2013;113:1099-101.
15. Claycomb WC, Lanson NAJ, Stallworth BS, et al. HL-1 cells: a cardiac muscle cell line that contracts and retains phenotypic characteristics of the adult cardiomyocyte. *Proc Natl Acad Sci U S A.* 1998;95:2979-84.
16. Morillo CA, Banerjee A, Perel P, et al. Atrial fibrillation: the current epidemic. *J Geriatr Cardiol.* 2017;14:195-203.
17. Sohns C, Marrouche NF. Atrial fibrillation and cardiac fibrosis. *Eur Heart J.* 2020;41:1123-31.
18. Gutierrez A, Chung MK. Genomics of atrial fibrillation. *Curr Cardiol Rep.* 2016;18:55.
19. Pérez-Serra A, Campuzano O, Brugada R. Update about atrial fibrillation genetics. *Curr Opin Cardiol.* 2017;32:246-52.
20. Lin H, Yin X, Xie Z, et al. Methylome-wide association study of atrial fibrillation in framingham heart study. *Sci Rep.* 2017;7:40377.
21. Poudel P, Xu Y, Cui Z, et al. Atrial fibrillation: recent advances in understanding the role of microRNAs in atrial remodeling with an electrophysiological overview. *Cardiology.* 2015;131:58-67.
22. Orenes-Piñero E, Montoro-García S, Patel J V, et al. Role of microRNAs in cardiac remodelling: new insights and future perspectives. *Int J Cardiol.* 2013;167:1651-9.
23. Wang Z, Lu Y, Yang B. MicroRNAs and atrial fibrillation: new fundamentals. *Cardiovasc Res.* 2011;89:710-21.
24. Zhao X, Wang Y, Sun X. The functions of microRNA-208 in the heart. *Diabetes Res Clin Pract.* 2020;160:108004.
25. Ikitimur B, Cakmak HA, Coskunpinar E, et al. The relationship between circulating microRNAs and left ventricular mass in symptomatic heart failure patients with systolic dysfunction. *Kardiol Pol.* 2015;73:740-6.
26. Kunert-Keil C, Bisping F, Krüger J, Brinkmeier H. Tissue-specific expression of TRP channel genes in the mouse and its variation in three different mouse strains. *BMC Genomics.* 2006;7:159.
27. Fonfria E, Murdock PR, Cusdin FS, et al. Tissue distribution profiles of the human TRPM cation channel family. *J Recept Signal Transduct Res.* 2006;26:159-78.
28. Jin J, Desai BN, Navarro B, et al. Deletion of *Trpm7* disrupts embryonic development and thymopoiesis without altering Mg²⁺ homeostasis. *Science.* 2008;322:756-60.
29. Du J, Xie J, Zhang Z, et al. TRPM7-mediated Ca²⁺ signals confer fibrogenesis in human atrial fibrillation. *Circ Res.* 2010;106:992-1003.
30. Diguat N, Trammell SAJ, Tannous C, et al. Nicotinamide riboside preserves cardiac function in a mouse model of dilated cardiomyopathy. *Circulation.* 2018;137:2256-73.
31. Yamamoto T, Byun J, Zhai P, et al. Nicotinamide mononucleotide, an intermediate of NAD⁺ synthesis, protects the heart from ischemia and reperfusion. *PLoS One.* 2014;9:e98972.
32. Byun J, Oka SI, Imai N, et al. Both gain and loss of *Nampt* function promote pressure overload-induced heart failure. *Am J Physiol Heart Circ Physiol.* 2019;317:H711-25.
33. Feng D, Xu D, Murakoshi N, et al. Nicotinamide phosphoribosyltransferase (*nampt*)/nicotinamide adenine dinucleotide (*nad*) axis suppresses atrial fibrillation by modulating the calcium handling pathway. *Int J Mol Sci.* 2020;21.
34. Brauch KM, Karst ML, Herron KJ, et al. Mutations in ribonucleic acid binding protein gene cause familial dilated cardiomyopathy. *J Am Coll Cardiol.* 2009;54:930-41.
35. Guo W, Schafer S, Greaser ML, et al. *RBM20*, a gene for hereditary cardiomyopathy, regulates titin splicing. *Nat Med.* 2012;18:766-73.
36. Filippello A, Lorenzi P, Bergamo E, Romanelli MG. Identification of nuclear retention domains in the *RBM20* protein. *FEBS Lett.* 2013;587:2989-95.
37. van den Hoogenhof MMG, Beqqali A, Amin AS, et al. *RBM20* mutations induce an arrhythmogenic dilated cardiomyopathy related to disturbed calcium handling. *Circulation.* 2018;138:1330-42.
38. Wells QS, Becker JR, Su YR, et al. Whole exome sequencing identifies a causal *RBM20* mutation in a large pedigree with familial dilated cardiomyopathy. *Circ Cardiovasc Genet.* 2013;6:317-26.
39. Lennermann D, Backs J, van den Hoogenhof MMG. New insights in *RBM20* cardiomyopathy. *Curr Heart Fail Rep.* 2020;17:234-46.



Protective Feature of Anzer Propolis in Contrast-Induced Nephropathy in Rats

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Abstract

Aim: The study aims to ascertain whether Anzer Propolis, a natural antioxidant compound, can protect the kidneys from iopromide.

Material and Method: This study was done in 2021. Four groups of 32 adult male Wistar albino rats, weighing between 250 and 300 g, were formed. Control (C) group contained eight rats. Intraperitoneal ethanol was administered to the Ethanol (E) group (n=8), 8 g/kg intraperitoneal iopromide to the contrast-induced nephropathy (CIN) group (n=8), and a 100 mg/kg dose of Anzer Propolis on the date of application to the Anzer Propolis group (AP) (n=8), as well as the prior day, by gastric gavage and then 8 g/kg iopromide was administered intraperitoneally. Termination was carried out at the 48th hour. Histopathological examination was performed for CIN in the right and left kidneys.

Results: Following has been examined as a part of the research: serum urea, creatinine, IL6, interleukin (IL)-1 β , total oxidant status (TOS), tumor necrosis factor (TNF- α), total antioxidant status (TAS), myeloperoxidase (MPO). TAS had a statistically significant increase in AP, in comparison to CIN, C and E groups (p<0.05). The pathological examination showed, vacuolar degeneration formations in tubular epithelial cells, and increase in mononuclear cell infiltration areas in the interstitial region in CIN. CIN had significantly higher values in comparison to AP (p<0.05).

Conclusion: Propolis protects the kidney tissue against the toxicity caused by CIN and negative effects of free radicals; most likely due to the antioxidant and antitoxic properties. Propolis is a promising natural substance for preventing CIN. There is a need for further research on the properties of propolis.

Keywords: Anzer propolis, contrast induced nephropathy, acute kidney injury, rat

INTRODUCTION

Contrast-induced nephropathy (CIN) is iatrogenic acute kidney injury that can emerge after administering iodinated contrast agent intravascularly for diagnostic imaging, interventional angiographic, or medical interventions (1). Although risk assessment and prevention strategies are applied for CIN before using iodinated contrast agents, it develops at a rate ranging from 1% to 25% in hospitalized patients and contributes to mortality and morbidity by increasing the length of hospital stay (2). Impaired renal perfusion are important in the pathogenesis of CIN (1,3). Iodinated contrast agents also increase oxidative stress by

lowering antioxidant enzyme levels, which increases the production of reactive oxygen species (ROS) or oxidative stress (4). It is aimed to reduce oxidative stress so as to prevent and treat CIN (1). For this purpose, antioxidant supplements, such as ascorbic acid, and medications, such as N-acetylcysteine and sodium bicarbonate, are used for prophylaxis and treatment in CIN (2,1).

Anzer Propolis, which contains honey and other bee products, is a frequently used substance in alternative medicine (5). The antioxidant, antitumor, and immunomodulatory effects of propolis have beneficial effects in treating various diseases (6-8).

CITATION

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The main antioxidant mechanism of propolis polyphenols is that ROS reduce the rate of the xanthine oxidase reaction. As a result, less free radicals are produced (9). Propolis efficiency is mainly related to its antioxidant and antitoxic properties. Previous studies showed that the ethanolic propolis extract contained important antioxidant compounds that inhibited ROS production (10-11).

Current investigation was done to determine how Anzer Propolis, which is indigenous to Türkiye's Eastern Black Sea Region, affected CIN.

MATERIAL AND METHOD

Following the US National Institutes of Health's Guidelines for the Care and Use of Laboratory Animals, all rats received compassionate treatment. The research was assigned the reference number 124-19 by Afyon Kocatepe University Experimental Animals Local Ethics Committee and granted approval on October 16, 2019. The Eastern Black Sea region of Türkiye is the only place where the endemic Anzer propolis employed in this research is found. This study was done in 2021.

Research Design

A standard climate environment was used to house 32 male Wistar albino rats that ranged in weight from 250 to 350 g. They were given free access to water and standard rat feed while being housed in individual cages. They had five days to adjust to the laboratory setting and later 4 groups of rats were created at random. All animals were manipulated in accordance with the US National Institutes of Health's Guidelines for the Care and Use of Laboratory Animals (NIH publication no. 85-23, was revised in 1996).

Contrast-Induced Nephropathy

The rats were dehydrated one day before the administration of iodinated contrast material in order to develop CIN. Intraperitoneally, 8 gr/kg iopromide (Ultravist 100 mL, Bayer, Berlin, Germany) was administered gradually. Regarding the occurrence of CIN, the clinical practice guidelines for Kidney Disease Improvement Global Outcomes (KDIGO) for acute kidney damage were taken as the basis. According to the KDIGO, CIN can be described as at least 0.3 mg/dL elevation (or 26.5 $\mu\text{mol/L}$) from baseline in serum creatinine (Cr) in the following 48 hours after contrast agent exposure or elevation that is more than 1.5x baseline within a week (7 days) after contrast agent exposure, or obtaining urine quantity that is less than 0.5 mL/(kg·h) at least six hours after the exposure (3).

Study Groups

The rats were designated into four groups to understand whether the results obtained in this study depended on the ethanol in the ethanolic propolis or the propolis substance.

Control group (group C, n=8): The rats were fed ad libitum and supplied with water. The rats were euthanized

according to established protocols after 48 hours.

Ethanol (group E, n=8): The rats were fed ad libitum and supplied with drinking water. On 0th day intraperitoneal (i.p.) ethanol was administered. The rats were euthanized according to established protocols after 48 hours, using high-dose anesthetics (150 mg/kg thiopental sodium).

Contrast-induced nephropathy group (group CIN, n=8): In this group, 8 g/kg iopromide (Ultravist, Bayer, Berlin, Germany) was injected intraperitoneally at a slow pace. The rats were euthanized according to established protocols after 48 hours as in group Ethanol.

Anzer propolis+contrast-induced nephropathy group (group AP, n=8): On the first day of the experiment, the rats in this group were gastric gavaged twice with 2 mL of saline and 100 mg/kg of propolis from the Anzer region that had been dissolved in ethanol. On day 0, the procedure was applied to CIN. The rats were sacrificed according to established protocols after 48 hours like the other groups. The animals were weighed on day 0 and at the end of 48 hours. Sacrificed rats' harvested kidneys were stored in 10% formol for histopathological examination.

Biochemical Analysis

Evaluation of renal functions

The values of urea, creatinine, and serum were measured using an autoanalyzer as the indicators of a decrease in glomerular functions, in blood samples obtained by an intracardiac puncture at the 48th hour.

Evaluation of neutrophil migration

Myeloperoxidase (MPO) activity was used to demonstrate the neutrophil infiltration in tissues. Rat MPO measurements were carried out by the ELISA method.

Biochemical measurements in blood samples

Determination of MPO, proinflammatory cytokines, and antioxidant status levels in serum

The serum MPO (Sunred Rabbit MPO ELISA Kit; Catalog No: YLA0057RB; Shanghai YL Biotech Co., Ltd., China), IL-1 β (Rat Interleukin-1 β , Catalog No: YLA 0031RA; Shanghai YL Biotech Co., Ltd., -China.), IL-6 (Rat Interleukin-6 Catalog No: YLA 0031RA; Shanghai YL Biotech Co., Ltd. -China.), TAS (Rat Total Antioxidant Status; Catalog No: YLA 1389 RA; Shanghai YL Biotech Co., Ltd., -China.), TOS (Rat Total Oxidant Status; Catalog No: (YLA 1392 RA; Shanghai YL Biotech Co., Ltd., China), and TNF- α (Rat Tumor necrosis alfa; ELISA Kit; E0764Ra) were analyzed by ELISA kits using MVGT Lambda Scan 200 (Bio-Tek Instrument, Winooski, VT, USA).

Measurement of the serum electrolyte level

An autoanalyzer (Roche Cobas 8000, Germany) was employed to measure the levels of serum K⁺, Ca⁺⁺, Na⁺, Cl⁻, and Mg⁺⁺ in blood samples taken at the 48th hour from all groups.

Hemogram measurement

The blood samples were obtained from the groups, and the hemogram was measured in a hemogram-measuring Cell Counter device (Huma Cell Count 80 TS).

Histopathological Evaluation

The 10% buffered neutral formaldehyde solution was used to fix the kidneys. After 48 hours, they were cut and transferred to cassettes for further tissue analysis. The tissues underwent a series of alcohol and xylene treatments before being blocked in paraffin. After that, blocks between 4 and 5 microns thick were cut using a microtome and mounted on slides. Following hematoxylin-eosin (HE) staining, the sections were examined under an optical microscope. The pathological changes in the kidneys were assessed and are presented in Table 1.

Degree	Damage	Pathological definition
0	None	Normal tubule
1	Light	Slight swelling and loss of brush-like edge
2	Light	Intense swelling and moderate vacuolization
3	Moderate	Nucleus shrinkage and severe vacuolization
4	Severe	Necrosis and rupture of the basal membrane of apoptotic cells
5	Necrosis	Tubular necrosis in its entirety

Statistical Analysis

Mean±standard deviation values were used to present the data, and to identify variations in the biochemical, electrolyte, and oxidative stress parameters, non-parametric ANOVA tests were employed. Furthermore, to determine the significance level a Tukey test was used. Microsoft's Statistical Package for Social Sciences (SPSS) version 24.0 was used to analyze the data (USA). It was deemed significant if $p < 0.05$.

RESULTS

The difference between the groups in serum urea and creatinine levels is shown in Table 2.

Compared to C, E, and AP, CIN's WBC levels significantly decreased ($p=0.000$). While the Hb level did not change for others, there was a significant increase in AP's Hb levels ($p=0.005$) (Table 3).

The differences between the groups for serum MPO, proinflammatory cytokines and antioxidant status levels are shown in Table 4.

The histopathological differences observed between the groups are shown in Table 5. The pathological examinations of all groups are shown in Figure 1.

Upon analysis, we discovered that Anzer Propolis utilized in the research contained high levels of ethyl oleate (10.23%), 5-hydroxy (9.07%), and 4H-1 benzopyran-4-one (12).

Groups	Creatinine mg/dL	Na ⁺ mmol/L	K ⁺ mmol/L	Cl ⁻ mmol/L	Ca ²⁺ mg/dL	Urea mg/dL	Mg ²⁺ mg/dL
C	0.37 ^b ±0.04	140.13±2.42	5.24 ^b ±0.28	99.80±0.58	9.75 ^b ±0.28	37.60 ^c ±0.65	2.69±0.27
E	0.44 ^a ±0.05	141.88±1.13	5.69 ^b ±0.25	99.78±1.53	10.45 ^a ±0.40	43.81 ^{ab} ±3.48	2.58±0.14
CIN	0.41 ^{ab} ±0.03	142.38±3.74	6.15 ^a ±0.62	101.04±2.77	10.24 ^a ±0.25	44.51 ^a ±4.72	2.57±0.11
AP	0.38 ^b ±0.03	141.50±1.60	5.62 ^b ±0.49	101.79±1.68	10.34 ^a ±0.29	40.36 ^{bc} ±3.63	2.47±0.20
P	0.008*	0.307	0.003*	0.093	0.001*	0.001*	0.165

K⁺: potassium; Cl⁻: chlorine; Ca²⁺: calcium; Mg²⁺: magnesium. *: $p < 0.01$; a, b, c: kidney function tests values ($p < 0.05$) with different letters in the same column are statistically significant

Groups	WBC 10 ⁹ /L	RBC 10 ¹² /L	HGB g/dL	HCT %	MCV fL	PLT 10 ⁹ /L
C	5.85 ^a ±0.73	9.02±0.49	15.73 ^b ±0.52	54.61 ^a ±2.29	54.61±2.29	690.25 ^b ±65.08
E	6.18 ^a ±1.69	9.16±0.36	15.58 ^b ±0.34	51.53 ^{bc} ±1.49	55.65±1.10	818.75 ^a ±50.38
CIN	3.32 ^b ±1.17	8.80±0.55	15.33 ^b ±0.70	49.43 ^c ±2.64	56.23±2.48	912.13 ^a ±117.73
AP	6.90 ^a ±1.79	9.40±0.26	16.48 ^a ±0.79	53.68 ^{ab} ±2.56	57.11±2.05	814.75 ^a ±134.14
P	0.000*	0.064	0.005*	0.000*	0.124	0.001*

Hb: hemoglobin, HCT: hematocrit, MCH: mean corpuscular hemoglobin, PLT: platelet, RBC: red blood count, WBC: white blood count; Hematological values ($p < 0.05$) with different letters in the same column are statistically significant

Table 4. Biochemical parameters in the groups (n=8) (Mean±SD)

Parameters/groups	CIN	E	AP	C	P value
TOS (U/mL)	5.5950±.21537 ^a	4.8638±.08401 ^b	4.7775±.13872 ^b	4.9525±.04636 ^b	0.001
TAS (U/mL)	11.0650±.43727 ^b	10.7500±.28069 ^b	12.9388±.25721 ^a	11.2437±.23140 ^b	0.001
IL-1β (ng/mL)	26.0250±1.65571 ^a	20.8525±1.15944 ^b	19.0463±.89201 ^{bc}	16.9063±.34428 ^c	0.001
IL-6 (ng/L)	35.0338±1.76343 ^a	19.5363±1.51576 ^c	25.0113±1.29203 ^b	20.9962±.59118 ^c	0.001
Hyp (ng/L)	260.0000±13.56203	271.5850±5.33029	289.6250±7.33372	281.4688±5.51215	0.110
MPO (ng/mL)	22.6013±.71762 ^a	16.3200±.41467 ^c	15.8700±.42172 ^c	18.0788±.22303 ^b	0.001
TNF-α (ng/mL)	44.6950±3.18151 ^a	25.9275±1.34338 ^b	23.0063±1.16015 ^b	24.2250±1.08938 ^b	0.001

Hyp: Hydroxyproline, IL-1: Interleukin-1, IL-6: interleukin-6, MPO: myeloperoxidase, TAS: total antioxidant status, TOS: total oxidant status, TNF: tumor necrosis factor. Letters next to biochemical parameters indicate statistical significance (p<0.05)

Table 5. Pathological evaluation of the groups (n=8)

Groups	Enlargement of the glomerular Bowman's space	Vacuolization formation in the glomerular capillary ball	Vacuolar degeneration formations in tubular epithelial cells	MNC infiltration areas in the interstitial region
C	0.00d±0.00	0.00d±0.00	0.00c±0.00	0.00b±0.00
E	0.88b±0.35	1.25b±0.46	1.00b±0.00	0.38b±0.52
CIN	1.88a±0.35	1.88a±0.35	2.25a±0.89	2.50a±0.76
AP	0.50c±0.53	0.75c±0.46	0.63b±0.52	0.38b±0.52
P	0.000*	0.000*	0.000*	0.000*

*: a, b, c, d: Letters next to renal histopathological values indicate statistical significance (p<0.05); MNC: mononuclear cell

DISCUSSION

Despite the risk assessment and prevention strategies for CIN before the use of iodinated contrast agents, it develops at a rate ranging from 1% to 25% of hospitalized patients. However, patients with high risk, like diabetics, geriatrics and those who suffer from chronic kidney diseases, this rate increases to 50%, increasing the length of hospital stay and contributing to mortality and morbidity (2,13). The pathogenesis of CIN is still not fully elucidated. However, there are various mechanisms suggested in the pathogenesis. These mechanisms are direct toxicity due to iodinated contrast agents, renal medullary hypoxia, and increased apoptosis (14). All these mechanisms cause increased oxidative stress, tissue damage and acute kidney injury. Iodized contrast agents increase oxidative stress through the increase of ROS production, or by decreasing antioxidant enzyme levels (6). For this reason, studies that aim to reduce oxidative stress were conducted to prevent the development of CIN (1,4,15). In this study, the protective properties of Anzer propolis against CIN were investigated biochemically and histopathologically.

Propolis is a natural substance broadly utilized both in folkloric and alternative medicine along with other bee products such as royal jelly, bee pollen, beeswax, and honey (5). Health benefits of propolis have been shown

in the treatment of various diseases resulting from its antiviral, antitumor, antioxidant, immunomodulatory, and anti-inflammatory effects (6-8). The main antioxidant mechanism of propolis polyphenols is that ROS and reactive nitrogen radical species (RNS) reduce the xanthine oxidase reaction. Thus, they reduce the formation of free radicals (9). Several investigation indicated that ethanolic propolis extract contains important antioxidant compounds can inhibit ROS production (10-11).

In our study, it was shown that serum creatinine level increased significantly in CIN and E, in comparison to C and AP (p=0.008). The similarity of serum creatinine levels in AP and C may be related to propolis phenols' nephroprotective properties due to their antioxidant and antitoxic properties. Likewise, in a previous experimental work of Baykara et al. (16), the nephroprotective effect of propolis against iodinated contrast agents was demonstrated. After administration of iodinated contrast, a significant increase in plasma urea level was observed in CIN, in comparison to C.

Nevertheless, AP's levels of plasma urea were significantly lower than CIN. Past studies reached similar conclusions (16-17).

Exposure to iodinated contrast agents triggers oxidative stress, increasing the production of ROS (14). In a previous

study, it has been shown that the TOS level increases and the TAS level decreases after application of iodinated contrast material (18). In our study, CIN's levels of TOS and TAS production were significantly higher than AP's. This result is related to the antioxidant and antitoxic properties of Anzer Propolis phenols (19).

In previous studies, it has been shown that CIN causes an increase in the level of interleukins (4,9). We observed significant decrease in IL-1 levels in AP, in comparison to E and CIN ($p<0.05$). Propolis has a rich content of flavonoids that inhibit nitric oxide, IL-1 and IL-6 production (20). It has been demonstrated that the acute phase reactant IL-6 contributes to renal autoimmune and inflammatory diseases by locally activating the classical and transsignal pathways. Podocytes, endothelial, mesangial, and tubular epithelial cells, among others, can be able to secrete IL-6 in kidneys (21). In the study of Hudzig B., et al. (22), there was an increase in patients' IL-6 levels who developed CIN. In our study, a statistically significant decrease in IL-6 levels was observed in AP and E, compared to CIN ($p<0.05$). The low levels of IL-1 and IL-6 in AP in our study may be due to the effect of flavonoids in AP content.

It has been shown that the level of MPO, a proinflammatory enzyme, increases in CIN (23). Increased MPO levels in the kidney are directly correlated with neutrophil infiltration and tissue inflammation brought on by contrast media. Activation of MPO can generate glomerular morphological changes, endothelial and mesangial cell damage and platelet activation, as well as glomerulonephritis (24). In our study, Anzer Propolis has been shown to reduce the level of MPO.

One of the proinflammatory mediators whose levels increase in contrast-related nephropathy is TNF α (25). It has been shown that the increase in TNF α level causes damage to renal tubular cells (26). In a single-center study, it was shown that the baseline level of TNF α is useful in demonstrating the prognosis in patients who develop CIN (27). For this reason, studies have been carried out to reduce the level of TNF α (25,26). In this study, Anzer propolis was shown to reduce TNF α level.

An increase in WBC level has been shown in contrast-related nephropathy (28). In the current study, WBC levels were statistically significantly higher in CIN and E than in AP ($p<0.05$). Anemia can trigger CIN progress by causing hypoxia due to reduced oxygen carrying capacity (29). Statistically significant increases were observed in hemoglobin and Hct values in AP compared to others ($p<0.05$). This result may be related to the antioxidant effect of Anzer Propolis.

The pathological effects of contrast agents on the kidneys are vacuolization in proximal epithelial cells, interstitial inflammation and cellular necrosis (30). In the pathological evaluation of our study, enlargement of the Bowman's space of the glomerulus in CIN, vacuolization formation in the glomerular capillary ball, vacuolar degeneration formations in the tubular epithelial cells and mononuclear

cell (MND) infiltration areas in the interstitial region were detected. These findings were significantly higher in CIN compared to AP ($p<0.05$). As a result of this pathological evaluation, it was revealed that AP protects kidney tissue with its antioxidant and antitoxic effects.

Since AP extract used in our study contains ethanol, it was revealed both biochemically and pathologically that the results obtained were related to the effect of AP, not ethanol.

CONCLUSION

CIN is iatrogenic acute kidney damage that prolongs hospital stays and increases mortality and morbidity. According to the literature, pathophysiological mechanisms leading to CIN have still not been fully explained. There are ongoing studies for preventing and treating CIN. Propolis protects the kidney tissue against the toxicity caused by CIN and negative effects of free radicals; most likely due to the antioxidant and antitoxic properties. Propolis is a promising natural substance for preventing CIN. There is a need for further research on the properties of propolis.

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Ethical approval: The research was assigned the reference number 124-19 by Afyon Kocatepe University Experimental Animals Local Ethics Committee.

REFERENCES

1. Kusirisin P, Chattipakorn SC, Chattipakorn N. Contrast-induced nephropathy and oxidative stress: mechanistic insights for better interventional approaches. *J Transl Med.* 2020;18:400.
2. Pattharanitima P, Tasanarong A. Pharmacological strategies to prevent contrast-induced acute kidney injury. *BioMed Res Int.* 2014;2014:236930.
3. Mehran R, Dangas GD, Weisbord SD. Contrast-associated acute kidney injury. *N Engl J Med.* 2019;380:2146-55.
4. Heyman SN, Rosen S, Khamaisi M, et al. Reactive oxygen species and the pathogenesis of radiocontrast-induced nephropathy. *Invest Radiol.* 2010;45:188-95.
5. Anjum SI, Ullah A, Khan KA, et al. Composition and functional properties of propolis (bee glue): a review. *Saudi J Biol Sci.* 2019;26:1695-703.
6. Kocot J, Kielczykowska M, Luchowska-Kocot D, et al. Antioxidant potential of propolis, bee pollen, and royal jelly: possible medical application. *Oxid Med Cell Longev.* 2018;2018:7074209.
7. Wolska K, Gorska A, Antosik K, et al. Immunomodulatory effects of propolis and its components on basic immune cell functions. *Indian J Pharm Sci.* 2019;81:575-88.
8. Chiu H-F, Han Y-C, Shen Y-C, et al. Chemopreventive and

- chemotherapeutic effect of propolis and its constituents: a mini-review. *J Cancer Prev.* 2020;25:70-8.
9. Kurek-Górecka A, Rzepecka-Stojko A, Górecki M, et al. Structure and antioxidant activity of polyphenols derived from propolis. *Molecules.* 2014;19:78-101.
 10. Asgharpour F, Moghadamnia AA, Motalebnejad M, et al. Propolis attenuates lipopolysaccharide-induced inflammatory responses through intracellular ROS and NO levels along with downregulation of IL-1 β and IL-6 expressions in murine RAW 264.7 macrophages. *J Food Biochem.* 2019;43:e12926.
 11. Song J-J, Lim HW, Kim K, et al. Effect of caffeic acid phenethyl ester (CAPE) on H₂O₂ induced oxidative and inflammatory responses in human middle ear epithelial cells. *Int J Pediatr Otorhinolaryngol.* 2012;76:675-9.
 12. Günday M, Saritaş ZK, Demirel HH, et al. Does anzer propolis have a protective effect on rabbit spinal cord ischemia/reperfusion injury?. *Braz J Cardiovasc Surg.* 2021;37:65-73.
 13. Finn WF. The clinical and renal consequences of contrast-induced nephropathy. *Nephrol Dial Transplant.* 2006;21:i2-10.
 14. Zhang F, Z Lu, F Wang. Advances in the pathogenesis and prevention of contrast-induced nephropathy. *Life Sci.* 2020;259:118379.
 15. Buyuklu M, Kandemir FM, Ozkaraca M, et al. Protective effect of curcumin against contrast induced nephropathy in rat kidney: what is happening to oxidative stress, inflammation, autophagy and apoptosis. *Eur Rev Med Pharmacol Sci.* 2014;18:461-70.
 16. Baykara M, Silici S, Özçelik M, et al. In vivo nephroprotective efficacy of propolis against contrast-induced nephropathy. *Diagn Interv Radiol.* 2015;21:317-21.
 17. Eraslan G, Kanbur M, Silici S, et al. Effects of cypermethrin on some biochemical changes in rats: the protective role of propolis. *Exp Anim.* 2018;57:453-60.
 18. Aksoy F, Baş HA, Bağcı A, Basri Savaş H. Predictive value of oxidant and antioxidant status for contrast-induced nephropathy after percutaneous coronary intervention for ST-segment elevation myocardial infarction. *Rev Port Cardiol (Engl Ed).* 2020;40:489-97.
 19. Oweis AO, Alshelleh SA, Daoud AK, et al. Inflammatory milieu in contrast-induced nephropathy: a prospective single-center study. *Int J Nephrol Renovasc Dis.* 2018;11:211-5.
 20. Wang K, Ping S, Huang S, et al. Molecular mechanisms underlying the in vitro anti-inflammatory effects of a flavonoid-rich ethanol extract from Chinese propolis (poplar type). *Evid Based Complement Alternat Med.* 2013;2013:127672.
 21. Nechemia-Arbely Y, Barkan D, Pizov G, et al. IL-6/IL-6R axis plays a critical role in acute kidney injury. *J Am Soc Nephrol.* 2008;19:1106-15.
 22. Hudzik B, Szkodzinski J, Danikiewicz A, et al. Serum interleukin-6 concentration predicts contrast-induced nephropathy in patients undergoing percutaneous coronary intervention. *Eur Cytokine Netw.* 2010;21:129-35.
 23. Al-Otaibi KE, Al Elaiwi AM, Tariq M, Al-Asmari AK. Simvastatin attenuates contrast-induced nephropathy through modulation of oxidative stress, proinflammatory myeloperoxidase, and nitric oxide. *Oxid Med Cell Longev.* 2012;2012:831748.
 24. Sela S, Shurtz-Swirski R, Cohen-Mazor M, et al. Primed peripheral polymorphonuclear leukocyte: a culprit underlying chronic low-grade inflammation and systemic oxidative stress in chronic kidney disease. *J Am Soc Nephrol.* 2005;16:2431-8. Erratum in: *J Am Soc Nephrol.* 2005;16:2814.
 25. Saritemur M, Un H, Cadirci E, et al. Tnf- α inhibition by infliximab as a new target for the prevention of glycerol-contrast-induced nephropathy. *Environ Toxicol Pharmacol.* 2015;39:577-88.
 26. Di Paola R, Genovese T, Impellizzeri D, et al. The renal injury and inflammation caused by ischemia-reperfusion are reduced by genetic inhibition of TNF- α R1: a comparison with infliximab treatment. *Eur J Pharmacol.* 2013;700:134-46.
 27. Banda J, Duarte R, Dix-Peek T, et al. Biomarkers for diagnosis and prediction of outcomes in contrast-induced nephropathy. *Int J Nephrol.* 2020;2020:8568139.
 28. Yamamoto Y, Yamamoto N, Kanematsu Y, et al. High white blood cell count is a risk factor for contrast-induced nephropathy following mechanical thrombectomy for acute ischemic stroke. *Cerebrovasc Dis Extra.* 2020;10:59-65.
 29. Xu J, Zhang M, Ni Y, et al. Impact of low hemoglobin on the development of contrast-induced nephropathy: a retrospective cohort study. *Exp Ther Med.* 2016;12:603-10.
 30. McCullough PA, Choi JP, Feghali GA, et al. Contrast-induced acute kidney injury. *J Am College Cardiol.* 2016;68:1465-73.



Are the Increased Frequency of Hand Washing After the COVID-19 Pandemic and Xerosis on the Hands Associated with the Occurrence of Hand Warts?

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Abstract

Aim: The COVID-19 pandemic has changed hand-washing habits. Exposure to water more frequently and time than normal causes dryness, dermatitis, and damage to the skin barrier. We aimed to investigate the relationship between the frequency and duration of exposure to water on the hands, obsession with hand washing, and warts on the hands.

Material and Method: A questionnaire was administered to hand warts group (n=94), plantar warts group (n=46), and healthy volunteers (n=30) questioning the factors that predispose to wart formation, hygiene behaviors, hand moisturizing habits, and hand washing obsession. The presence of warts, localization, number, and clinical type, presence of xerosis, and hand dermatitis were recorded. Data from the hand warts group were compared with control groups of healthy volunteers with plantar warts.

Results: The total exposure time of the hands to water per day was significantly higher in hand warts group than in the plantar warts group and healthy ones (<0.001, both). While xerosis was observed in 51.1% of the hand warts group, further clinical evaluation was recommended with the suspicion of handwashing obsession in 26.6%. The suspicion of handwashing obsession was reinforced by bilateral warts, hand dorsum involvement, more than one anatomical region involvement, and a high number of warts (p=0.039, p=0.048, p=0.027, p=0.018; respectively).

Conclusion: Water exposure might be a novel unrecognized risk factor for hand warts. Patients with hand warts should be evaluated regarding OCD and the need for moisturizer by questioning the frequency of handwashing.

Keywords: Wart, hand washing, xerosis, nail-biting, obsessive-compulsive disorder

INTRODUCTION

Cutaneous warts are mucocutaneous lesions caused by the human papillomavirus (HPV). According to the site of involvement and morphology, they are classified by different nomenclatures such as verruca vulgaris, verruca plana, verruca plantaris, and condyloma acuminata (1). Cutaneous warts are a common viral infection in the general population, especially in children. One-third of primary school children have one or more warts on their hands or feet, with an incidence of 29 per 100 person-years for developing new warts (2). The estimated prevalence of warts has been reported to be 33% in children aged 6-12 years and 3.5% in adults (3). It is a usual reason for dermatology outpatient clinic applications.

Transmission of infection usually occurs through direct

contact or, more rarely, through contaminated objects (4). Infection occurs when the virus penetrates through a damaged epithelial barrier, especially in poorly perfused areas such as the hands, fingers, or feet. Microtraumas expose basal layer keratinocytes and facilitate transmission (5). HPV infecting basal cells causes abnormal acceleration of the cell cycle and the emergence of neoplasia. Immunosuppression, close contact with family members with warts, handling meat, walking barefoot for plantar warts, nail-biting, and palmoplantar hyperhidrosis are predisposing factors (6-9). The more frequent hand warts in some occupational groups have been attributed to trauma in some studies (3,6).

It is clear that washing hands with soap and water is crucial for protection from viruses and bacteria, contamination

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control, and sanitation (10). Hand hygiene practices began to be widely implemented after the COVID-19 outbreak. Washing hands with soap and using alcohol-based hand sanitizer is known to reduce the spread of the virus (11).

However, more frequent and more prolonged exposure to water than usual causes xerosis, dermatitis, and damage to the skin barrier on the hands (12). Prolonged exposure of hands to water can be caused by various occupational reasons such as dishwashing, housewife, babysitting, cleaning, hairdressing, or various psychiatric reasons such as anxiety and obsessive-compulsive disorder (OCD) (13,14). Although it is sensible that the factors increasing the risk of xerosis on the hands may also predispose to hand warts, the best of our known, no study has been done on this subject.

This study aimed to investigate the relationship between the frequency and duration of exposure to water on the hands due to various reasons and warts on the hand.

MATERIAL AND METHOD

Patients and Study Design

The study was conducted with participants aged 15-45, between April and September 2021, when the weather is milder in our geography, to minimize the seasonal effect on xerosis. Approval for the study was granted by the Erzurum Atatürk University Clinical Research Ethics Committee, (reference no: B.30.2ATA.0.01.00/335). Informed consent forms were obtained from all participants. The study was performed per the latest version of the "Helsinki Declaration" and the "Guidelines for Good Clinical Practice."

Patients with verruca vulgaris only on their hands and only on their plantar regions and healthy individuals who have never had warts were recruited for the study. It was reported that warts in family members and schoolmates are a risk factor for transmission (15). In order to adjust the groups in terms of family history of warts, some of the healthy individuals were selected from the relatives of other patients who presented with verruca vulgaris. This selection of healthy volunteers was intended to reinforce the assumption of exposure to HPV. Patients with plantar warts and healthy individuals were considered two separate control groups in the study. The reasons for attributing patients with plantar warts to the control group were the reduction of the risk of type 1 statistical error and the fact that the feet are end organs with perfusion characteristics similar to the hands.

Participants' sociodemographic data, current number, localization and distribution of warts, complaint duration, family history, and the number seeking treatment were recorded. While the number of handwashing, water exposure length, soap usage, and disinfectant exposure were recorded, some questions with dichotomous (Yes/No) answers were asked to the patient to screen for the presence of a cleaning obsession: Do you think you have a cleaning obsession?/Do you feel the urge to wash your

hands repeatedly after washing them? / Does your hand washing or cleaning job take up hours? / Does the feeling of contamination occupy your mind all the time? Patients suspected of handwashing obsession were referred to psychiatry. Also, the nail-biting/onychophagia behavior of all participants was questioned.

Exclusion criteria from the study were as follows: Palmoplantar hyperhidrosis, history of frequent exposure to irritant agents other than water or soap, atopic dermatitis, allergic contact dermatitis, presence of any systemic disease or regular supplementary food products or drug use, immunosuppression, topical steroid/calcineurin inhibitory use of inhibitor, the simultaneous presence of concomitant warts in distant localization from the relevant area. Besides, patients with subungual warts were not included in the study.

Statistical Analysis

All procedures were performed using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA, v21.0) software. After checking the normality distribution of scale variables by Kolmogorov-Smirnov test, continuous parameters were compared using Kruskal-Wallis H and Mann-Whitney U tests according to the number of samples. The exact significance test for the Mann-Whitney U test was performed when the sample size was insufficient. Pearson's chi-square or Fisher's exact tests compared independent categorical variables according to the sample sizes. Continuous variables were stated as mean±standard deviation or median (interquartile range), and categorical variables as numbers (percentages). Bonferroni correction was applied post-hoc if significant results were obtained in more than two-sample comparisons. The p-values achieved after post-hoc analysis were tabulated in an adjusted manner. A two-sided p-value<0.05 was considered statistically significant.

RESULTS

One hundred and seventy individuals participated in the study: hand warts (n=94), plantar warts (n=46), and healthy individuals (n=30). The study groups were similar in terms of age and gender (p=0.172, p=0.881; respectively). Comparisons of some data of patients with hand warts with the other two separate control groups (patients with plantar warts and healthy individuals) were presented in Table 1. The sociodemographic and clinical characteristics of the patients, the use of water, soap, disinfectant, and moisturizer, the presence of xerosis in the hands, the suspicion of handwashing obsession, and the nail-biting behavior were compared in Table 1. There was no difference between those with hand and plantar warts in terms of the total number and distribution of warts. The frequency of handwashing was significantly higher in patients with hand warts than in both plantar warts and healthy controls (p<0.001; post-hoc: adjusted p<0.001, adjusted p=0.046; respectively). Similarly, the total exposure time of the hands to water per day was

significantly higher in patients with hand warts than in plantar warts and healthy ones (<0.001 ; post-hoc: adjusted $p<0.001$, adjusted $p=0.001$; respectively). On the other hand, there was no difference between the groups

regarding the use of moisturizer ($p>0.05$). No relationship was found between hand warts and nail-biting behavior ($p=0.828$).

Table 1. Comparison of some data of patients with hand warts and 2 separate control groups consisting of healthy individuals and those with plantar warts

Parameters		Patient group		Control groups		p-value
		Warts on hands (A; n=94)	Plantar warts (B; n=46)	Healthy individuals (C; n=30)		
Age, years		25.3±7.8	24.4±5.7	27.8±7.5		0.172
Sex	Man	47 (50.0%)	25 (54.3%)	15 (50.0%)		0.881
	Woman	47 (50.0%)	21 (45.7%)	15 (50.0%)		
Education level	Middle school & below	19 (20.2%)	8 (17.4%)	6 (20.0%)		0.921
	Secondary school & above	75 (79.8%)	38 (82.6%)	24 (80.0%)		
Direction of warts	Unilateral	54 (57.4%)	31 (67.4%)	-		0.258
	Bilateral	40 (42.6%)	15 (32.6%)	-		
Total number of warts		5.3±6.1	4.6±4.5	-		0.723
Complaint length; months		12.9±15.1	8.9±8.1	-		0.335
Family history of warts; Yes		29 (30.9%)	14 (34.1%)	11 (36.7%)		0.775
Number of seeking treatment for warts		2.4±2.6	2.3±2.0	-		0.928
Number of handwashing per day		12.5±8.6	7.3±3.5	8.0±3.1		<0.001^{ab}
Total daily water exposure time to hands; min. (including handwashing and all other activities)		33.1±37.1	16.5±23.1	11.0±9.6		<0.001^{ab}
Reasonable and mandatory occasion for water exposure to hands (e.g., job, hobby)	Yes	11 (11.7%)	3 (6.5%)	5 (16.7%)		0.379
	No	83 (88.3%)	43 (93.5%)	25 (83.3%)		
Soap type	Bar	23 (24.5%)	16 (34.8%)	5 (16.7%)		0.190
	Liquid	71 (75.5%)	30 (65.2%)	25 (83.3%)		
Total number of disinfectant usages per day		3.5±3.0	2.9±2.9	3.9±3.7		0.220
Habit of using any moisturizer	Never	34 (36.2%)	19 (41.3%)	15 (50.0%)		0.434
	Rarely	36 (38.3%)	18 (39.1%)	12 (40.0%)		
	Regularly	24 (25.5%)	9 (19.6%)	3 (10.0%)		
Frequency of using a moisturizer per day for regular users (n=36)		2.0±1.9 (n=24)		2.4±1.4 (n=12)		0.129
Xerosis cutis on the hands	Yes	48 (51.1%)	11 (23.9%)	6 (20.0%)		0.001^{ab}
	No	46 (48.9%)	35 (76.1%)	24 (80.0%)		
Irritant dermatitis on the hands	Yes	13 (13.8%)	3 (6.5%)	1 (3.3%)		N/A
	No	81 (86.2%)	43 (93.5%)	29 (96.7%)		
Suspicion of handwashing obsession	Yes	25 (26.6%)	2 (4.3%)	0 (0.0%)		0.001^{ab}
	No	69 (73.4%)	44 (95.7%)	30 (100.0%)		
Presence of nail biting/onychophagia behavior	Yes	22 (23.7%)	9 (19.6%)	6 (20.0%)		0.828
	No	71 (76.3%)	37 (80.4%)	24 (80.0%)		
Total number of actions per day in those with nail biting behavior (n=37)		7.5±9.8 (n=22)		6.9±9.9 (n=15)		0.897

Min.: minute, Data are expressed as mean±standard deviation or number of patients (percentage). Kruskal-Wallis H, Mann-Whitney U, and Pearson chi-square tests were used, where is appropriate. Bonferroni correction was applied as post-hoc if significant results were obtained in more than two-sample comparisons. Significant values were shown in bold. Superscript a for the difference between A and B groups; superscript b for the difference between A and C groups; superscript c for the difference between B and C groups

The relationship between the distribution and number of warts on the hand and the presence of xerosis, suspicion of handwashing, and nail-biting behavior is presented in Table 2. Accordingly, xerosis was significantly more common in older patients with hand warts and those who washed their hands more frequently ($p=0.006$, $p=0.022$; respectively). Dorsum involvement was significantly more common in patients with warts on xerotic hands ($p=0.014$). While xerosis was observed in 51.1% of the patients with

hand warts, further clinical evaluation was recommended with the suspicion of handwashing obsession in 26.6%. In patients presenting with hand warts, the suspicion of handwashing obsession was reinforced by bilateral warts, hand dorsum involvement, more than one anatomical region involvement, and a high number of warts ($p=0.039$, $p=0.048$, $p=0.027$, $p=0.018$; respectively). No correlation was found between nail-biting behavior and the distribution and number of warts on the hands ($p>0.05$).

Table 2. The relationship between the distribution and number of warts on the hand and the presence of xerosis, suspicion of handwashing obsession and nail-biting behavior

Parameters	Xerosis cutis on the hands		Suspicion of handwashing obsession		Nail-biting behavior		p-value	
	Yes (n=48)	No (n=46)	Yes (n=25)	No (n=69)	Yes (n=22)	No (n=71)		
Age, years; Med (IQR)	24 (12)	20 (5)	22 (10)	22 (9)	20.5 (5)	22 (11)	0.117	
Sex; n (%)	Man	24 (50.0%)	23 (50.0%)	9 (36.0%)	38 (55.1%)	10 (45.5%)	37 (52.1%)	0.585
	Woman	24 (50.0%)	23 (50.0%)	16 (64.0%)	31 (44.9%)	12 (54.5%)	34 (47.9%)	
Direction of warts on the hands; n (%)	Unilateral	28 (58.3%)	26 (56.5%)	10 (40.0%)	44 (63.8%)	13 (59.1%)	41 (57.7%)	0.911
	Bilateral	20 (41.7%)	20 (43.5%)	15 (60.0%)	25 (36.2%)	9 (40.9%)	30 (42.3%)	
Periungual inv.; only; n (%)	10 (20.8%)	9 (19.6%)	3 (12.0%)	17 (24.6%)	5 (22.7%)	13 (18.3%)	0.758 ‡	
Combined inv. co-existing periungual inv.; n (%)	11 (22.9%)	12 (26.1%)	9 (36.0%)	14 (20.3%)	5 (22.7%)	18 (25.4%)	0.803	
Periungual inv.; combined or only	n (%)	21 (43.8%)	21 (45.7%)	11 (44.0%)	31 (44.9%)	10 (45.5%)	31 (43.7%)	0.882
	Med (IQR)	2 (3)	2 (4)	2 (7)	2 (2)	1.5 (5)	2 (2)	0.709 †
Periungual and/or finger inv.	n (%)	23 (62.2%)	28 (66.7%)	14 (66.7%)	37 (63.6%)	11 (57.9%)	39 (66.1%)	0.517
	Med (IQR)	2 (3)	2 (2.5)	2 (7.25)	2 (2.5)	2 (6)	2 (2)	0.816
Dorsum of the hands; only; n (%)	n (%)	12 (25.0%)	3 (6.5%)	4 (16.0%)	11 (15.9%)	3 (13.6%)	12 (16.9%)	1.000 ‡
	Med (IQR)	10 (20.8%)	12 (26.1%)	9 (36.0%)	12 (17.3%)	4 (18.2%)	18 (25.4%)	0.489
Dorsum inv. co-existing dorsum inv.; n (%)	n (%)	22 (45.8%)	15 (32.6%)	13 (52.0%)	24 (34.8%)	7 (31.8%)	30 (42.3%)	0.382
	Med (IQR)	3 (7)	3 (3)	3 (9)	2.5 (4)	2 (2)	3 (5)	0.481 †
Palm and/or finger inv.; n (%)	n (%)	13 (27.1%)	16 (34.8%)	6 (24.0%)	23 (33.3%)	7 (31.8%)	22 (31.0%)	0.941
	Med (IQR)	11 (22.9%)	16 (34.8%)	6 (24.0%)	15 (21.7%)	6 (27.3%)	21 (29.6%)	0.835
Palm and/or finger inv. combined or only	n (%)	24 (50.0%)	32 (69.6%)	18 (72.0%)	38 (55.1%)	13 (59.1%)	43 (60.6%)	0.902
	Med (IQR)	3 (5)	2 (3)	2 (3)	2 (3)	2 (1.5)	2 (3.5)	0.614
Inv. in multiple hand region	n (%)	14 (29.2%)	18 (39.1%)	13 (52.0%)	19 (22.5%)	7 (31.8%)	25 (35.2%)	0.770
	Med (IQR)	9 (18)	6 (12)	11 (10)	5 (6)	5 (11)	7 (10)	0.656 †
Total number of warts	Med (IQR)	3 (6)	3 (4)	5 (11)	3 (4)	2 (5)	3 (5)	0.211
	Complaint length; months; Med (IQR)	12 (21)	6 (10)	12 (20)	6 (10)	9 (10)	9 (21)	0.392
Number of seeking treatment for warts; Med (IQR)	2 (1)	2 (1)	1 (1)	2 (1)	1 (1)	2 (1)	2 (1)	0.203
	Number of handwashing per day; Med (IQR)	15 (14)	9 (5)	17.5 (5)	8 (7)	6 (15)	10 (9)	0.206
Total daily water exposure time to hands, minutes; Med (IQR)	20 (35)	17.5 (20)	45 (30)	10 (25)	17.5 (21)	20 (35)	0.658	
	Yes	8 (17.0%)	14 (30.4%)	9 (37.5%)	13 (18.8%)	-	-	-
Presence of nail biting/onychophagia behavior; n (%)	No	39 (83.0%)	32 (69.6%)	15 (62.5%)	56 (81.2%)	-	-	0.064

Med (IQR): Median (Interquartile range); Inv: Involvement, Data are expressed as median (interquartile range) or number of patients (percentage). Mann-Whitney U, Pearson chi-square, and Fisher's exact † tests were used, where is appropriate. Exact significance test † for Mann-Whitney U test was performed when the sample size was not sufficient. Significant values were shown in bold

Dermatologists' opinions on handwashing habits and moisturizing requirements for patients with hand warts were distributed as in Figure 1. In 19.1% of patients with hand warts, it was necessary to make behavioral recommendations to change frequent or prolonged handwashing habits in addition to moisturizers. Apart from this, the opinion that only moisturizer should be recommended in 23.4% of the patients was adopted.

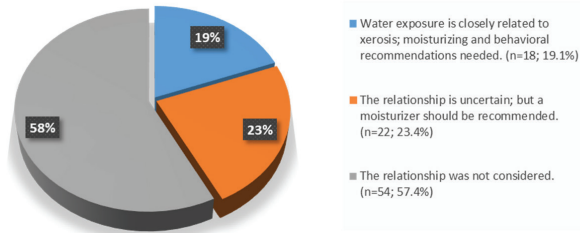


Figure 1. Dermatologists' opinions on handwashing habits and moisturizing requirements for patients with hand warts

DISCUSSION

The main risk factors for skin infections are age, sex, ethnicity, medical history, family history, local climate, lifestyle, and hygiene habits (6). However, studies evaluating the relationship between viral warts and hygiene habits are lacking. One of the most important causes of hand eczema is water exposure and alcohol-based hand rubs. The clinical presentation includes rough, dry, scaly skin, erythema, and a burning sensation (16). Also, it may develop clinically as dryness and roughness in the hands without dermatitis after exposure to water. Irritant contact dermatitis can be seen with a frequency of 17-30% in cases of occupational predisposition such as housewives and healthcare workers; compared to the general population with a prevalence of 5.4% (16-18). In this study, the groups were similar in terms of the existence of a reasonable and necessary condition, such as a job or hobby, to explain the exposure to water. Since our study was conducted during the COVID-19 pandemic period, we found that handwashing frequency, duration, and disinfectant use were relatively high in the patient and control groups. However, handwashing frequency, daily water exposure time, and xerosis cutis on the hands were significantly higher in patients with hand warts than in plantar and healthy controls. Xerosis was observed in 51.1% of patients with hand warts, and dorsum involvement was significantly higher in xerotic hands. As dermatologists, we considered that 42.6% of the patients with hand warts might have an uncertain relationship with xerosis.

The estimated prevalence of OCD in the United States has been reported to be 2.3% for lifetime and 1.2% for one-year criteria (19). The most common obsessive thoughts are pollution, contamination, and the risk of infection. The most common compulsive behaviors are cleaning/washing, checking, repeating, counting, and ordering/arranging (20). Contamination obsessions and cleaning/washing compulsions are seen in cleaning OCD. Therefore, it is not surprising that hand dermatitis is one of the

most common symptoms in patients with cleaning OCD. Studies have shown that OCD patients begin psychiatric treatment only 8-10 years after the first symptoms. In this period, dermatological symptoms and findings generally become chronic (21). Various studies have revealed that 9% to 35% of patients with OCD consult a dermatologist with skin conditions such as dermatitis, hand eczema, and lichen simplex chronicus before psychiatry (22). We realized that warts on the hands have never been evaluated in this respect in the studies. Suspicion of handwashing obsession was significantly more common, especially in those with warts on their hands than in those with plantar warts and healthy ones in this study. As a dermatologist, we think that 26.6% of patients with warts on their hands deserve further evaluation in terms of OCD, and hand dryness was clearly associated with handwashing habits in 19.1%. These data suggest that hand warts accompanying dryness and roughness on the hands are also an indicator reinforcing the suspicion of OCD. Indeed, we found that bilateral involvement, involvement of more than one anatomical hand region, and increased number of warts in patients with hand warts reinforce the suspicion of OCD.

Nail-biting is a compulsive behavior common among children and young adults. It seems to be associated with OCD and usually occurs with psychopathological symptoms (23,24). It has been reported that cuticle peeling and nail-biting behaviors increase the risk of subungual warts (9). This study did not confirm our assumption that nail-biting may be associated with the number and presence of periungual warts. Besides, nail-biting behavior did not affect the distribution and number of warts on the hands. However, the exclusion of those with atopic dermatitis, allergic contact dermatitis, immunodeficiency, and systemic disease in our study shows that nail-biting alone may not be a potential risk factor for hand warts.

Kampf and Ennen emphasized that in case of repeated and frequent hand washing, the regular use of a moisturizer immediately after hand washing prevents hand drying. Especially in subjects with dry skin, it was observed that the skin condition improved despite intensive washing (25). Symanzik et al showed that in the presence of frequent and repetitive hand washing, the use of a moisturizer immediately after washing and the use of syndet have positive effects on epidermal barrier homeostasis. Their findings imply the effect of using syndet and moisturizer as part of treatment in patients with warts on xerotic hands, especially those with prolonged water exposure (26). In our study, the fact that there was no difference between the groups regarding moisturizer usage habits indicates the necessity of recommendation in this regard.

CONCLUSION

Our study revealed that water exposure might be a novel unrecognized risk factor for hand warts, possibly facilitating transmission by disrupting the skin barrier and increasing the effect of microtraumas. In the presence of warts on the hands, the patients should be evaluated

regarding OCD and the need for moisturizer by questioning the frequency of handwashing. We think that this will contribute to the early detection of OCD patients. In addition, the use of moisturizers and changes in hygiene habits may contribute to the success of the treatment of hand warts. Further studies with larger sample sizes should support our results.

Study Limitations

Although this is the first study on this subject, its limitations should be noted. The sample size is relatively small. Therefore, the relationship between warts and hand eczema could not be evaluated statistically. Due to technical impossibility, trans-epidermal water loss (TEWL) could not be measured. Xerosis on the hands is determined subjectively by the physicians' opinion. In addition, the study was conducted during the pandemic period. This situation may have caused an increase in the frequency of xerosis, eczema, and OCD suspicion. Although patients with suspected OCD were referred to psychiatry, the psychiatrist's opinion could not be interpreted due to the disruption in patient follow-up. However, patient selection criteria and the prospective design of our study allowed us to interpret our results under optimal conditions

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Ethical approval: *This study was approved by the Ethics Committee of Erzurum Atatürk University (reference no: B.30.2ATA.0.01.00/335) and conducted according to the Helsinki Declaration of Human Rights.*

REFERENCES

- Goldsmith LA, Katz SI, Gilchrist BA, et al. Fitzpatrick's Dermatology. in General Medicine. 8nd edition. McGrawHill Medical, 2012;2421-9.
- Ghorzang E, de Koning MNC, Bouwes Bavinck JN, et al. HPV type-specific distribution among family members and linen in households of cutaneous wart patients. J Eur Acad Dermatol Venereol. 2022;36:119-25.
- Ghadgepatil SS, Gupta S, Sharma YK. Clinicoepidemiological study of different types of warts. Dermatol Res Pract. 2016;2016:7989817.
- Magalhães GM, Vieira ÉC, Garcia LC, et al. Update on human papilloma virus-part I: epidemiology, pathogenesis, and clinical spectrum. An Bras Dermatol. 2021;96:1-16.
- Egawa N, Egawa K, Griffin H, et al. Human papillomaviruses; epithelial tropisms, and the development of neoplasia. Viruses. 2015;7:3863-90.
- Konishi L, Alfredo CH, Silva-Junior JS. Hand warts among butchers in a supermarket in São Paulo. Rev Bras Med Trab. 2018;16:451-6.
- Sterling JC, Handfield-Jones S, Hudson PM. Guidelines for the management of cutaneous warts. Br J Dermatol. 2001;144:4-11.
- Mulhem E, Pinelis S. Treatment of nongenital cutaneous warts. Am Fam Physician. 2011;84:288-93.
- Halteh P, Scher RK, Lipner SR. Onychophagia: a nail-biting conundrum for physicians. J Dermatolog Treat. 2017;28:166-72.
- World Health Organization. Interim recommendations on obligatory hand hygiene against transmission of COVID-19. <https://www.who.int/publications/m/item/interim-recommendations-on-obligatory-hand-hygiene-against-transmission-of-covid-19> access date 01.04.2020.
- Loh EW, Yew YW. Hand hygiene and hand eczema: a systematic review and meta-analysis. Contact Dermatitis. 2022;87:303-14.
- Metin N, Turan Ç, Utlu Z. Changes in dermatological complaints among healthcare professionals during the COVID-19 outbreak in Turkey. Acta Dermatovenerol Alp Pannonica Adriat. 2020;9:115-22.
- Meding B, Anveden Berglind I, Alderling M, et al. Water exposure—challenging differences between occupations. Contact Dermatitis. 2016;74:22-8.
- Mavrogiorgou P, Bader A, Stockfleth E, Juckel G. Obsessive-compulsive disorder in dermatology. JDDG: Journal der Deutschen Dermatologischen Gesellschaft. 2015;13:991-1000.
- De Koning M, Quint K, Bruggink S, et al. High prevalence of cutaneous warts in elementary school children and the ubiquitous presence of wart-associated human papillomavirus on clinically normal skin. Br J Dermatol. 2015;172:196-201.
- Smit H, Burdorf A, Coenraads P. Prevalence of hand dermatitis in different occupations. Int J Epidemiol. 1993;22:288-93.
- Kavli G, Angell E, Moseng D. Hospital employees and skin problems. Contact Dermatitis. 1987;17:156-8.
- Meding B, Swanbeck G. Epidemiology of different types of hand eczema in an industrial city. Acta Derm Venereol. 1989;69:227-33.
- Ruscio AM, Stein DJ, Chiu WT, Kessler RC. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. Mol Psychiatry. 2010;15:53-63.
- Osland S, Arnold PD, Pringsheim T. The prevalence of diagnosed obsessive compulsive disorder and associated comorbidities: a population-based Canadian study. Psychiatry Res. 2018;268:137-42.
- García-Soriano G, Rufer M, Delsignore A, et al. Factors associated with non-treatment or delayed treatment seeking in OCD sufferers: a review of the literature. Psychiatry Res. 2014;220:1-10.
- Sheikhmoonesi F, Hajheidari Z, Masoudzadeh A, et al. Prevalence and severity of obsessive-compulsive disorder and their relationships with dermatological diseases. Acta Med Iran. 2014;52:511-4.
- Pacan P, Grzesiak M, Reich A, Szepletowski JC. Onychophagia as a spectrum of obsessive-compulsive disorder. Acta Derm Venereol. 2009;89:278-80.
- Richert B, André J. Nail disorders in children: diagnosis and management. Am J Clin Dermatol. 2011;12:101-12.

25. Kampf G, Ennen J. Regular use of a hand cream can attenuate skin dryness and roughness caused by frequent hand washing. *BMC Dermatol* 2006;6:1.
26. Symanzik C, Kezic S, Jakasa I, et al. Effects of skin washing frequency on the epidermal barrier function and inflammatory processes of the epidermis: an experimental study. *Contact Dermatitis*. 2022;87:241-6.



Examination of Pain, Quality of Life, Disability, and Anxiety in Patients Undergoing Lumbar Disc Surgery with and without COVID-19

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Abstract

Aim: This study aims to examine pain, disability, anxiety, and quality of life in patients undergoing lumbar disc herniation (LDH) surgery with and without COVID-19.

Material and Method: Eighty patients who were diagnosed with LDH and planned surgery between March and September 2023 were included in the study. 50% of the patients were diagnosed with COVID-19 for at most six months, according to the positive polymerase chain reaction (PCR) test. 50% of the patients had no symptoms of COVID-19, ranging from mild to severe, and the PCR test was negative (-). The patients' pain level, disability, anxiety, and quality of life were evaluated and compared between the groups with and without COVID.

Results: The mean scores of physical roles, physical function, mental health, body pain, and social function on the SF-36 quality of life scale in the LDH+COVID-19 (+) patient group were significantly lower than those in LDH+COVID-19 (-) ($p<0.05$). Additionally, a statistically significant difference was observed between pain, anxiety, and disability levels in favor of the LDH+COVID-19 (+) patient group ($p<0.05$).

Conclusion: Patients with COVID-19 undergoing LDH surgery have poor quality of life with high levels of anxiety, pain, and disability. Therefore, it is important to consider the current results during the postoperative rehabilitation process.

Keywords: Lumbar disc, COVID-19, anxiety, quality of life, pain

INTRODUCTION

Low back pain is a problem that affects approximately 80% of people at some point in their lives (1). Various factors cause this situation. However, low back pain due to degenerative joint and disc disease is relatively less common (2). Lumbar disc herniation (LDH) is a pathology characterized by a change in the discs' normal position due to discs' overload during the degeneration process (3,4). Mechanical and inflammatory processes are considered important factors in forming low back pain (5). Incorrect movements, overload, or physical inactivity also affect the load-bearing capacity of the spine and cause disc lesions (4,5). Irritation and inflammation resulting from compression of peripheral nerves between intervertebral discs following disc lesions is the accepted theory for the

origin of pain (6,7).

During the COVID-19 epidemic, many precautions were taken to control it. Social isolation has also increased due to travel restrictions and compliance with interpersonal distance rules. As a result, there has been an increase in loneliness rates, and this has led to the deterioration of both mental and physical health worldwide (8,9). When pain is evaluated from a biopsychological perspective, loneliness and isolation are the most well-known causes of pain exacerbation among psychosocial factors (10). Studies report that an increase in loneliness and social isolation may be associated with high levels of pain (10-12). There has been an increase in psychological stress rates due to increased loneliness and social isolation in the COVID-19 epidemic, and this has triggered pain,

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leading to an effective potential in individuals with chronic pain (11,12). When the literature is examined, it has also been shown that patients' quality of life after COVID-19 is seriously affected (13,14).

Studies have shown that increased social isolation because of COVID-19 measures may be associated with psychological stress, pain, and quality of life (10-14). This situation also results in physical inactivity and increases problems such as low back pain (11). Additionally, it may increase LDH symptoms. However, when the literature is examined, there is no direct evidence of a relationship between psychosocial factors after LDH surgery and a history of COVID-19 infection. Our hypothesis in our study is that there may be an increase in the degree of disability and pain symptoms after COVID-19 infection in patients who underwent LDH surgery. In this context, this study aims to compare the pain, quality of life levels, disability and anxiety of patients who underwent LDH surgery according to their COVID-19 infection status.

MATERIAL AND METHOD

This cross-sectional study included patients scheduled for LDH surgery referred to the neurosurgery outpatient clinic of Karabük University Training and Research Hospital between March 2022 and September 2023. Forty female and forty male patients were included in the study. Patients whose diagnosis of intervertebral disc pathology was confirmed by MRI after evaluation by a neurosurgeon who was over 18 years of age and who volunteered to participate in the study were included. Additionally, patients who had or had not had COVID in the last six months, according to the positive polymerase chain reaction test, were included in the study. Patients who were pregnant, had lumbar degenerative changes (spondylolisthesis, scoliosis, malignancy, vertebral fracture, osteoporosis, lumbar osteoarthritis, etc.) in the MRI report, had other musculoskeletal diseases in addition to low back pain, had fibromyalgia, and had a primary psychiatric disease were excluded from the study.

The number of individuals to participate in the study was determined by the G*Power program. According to the pain results of the pilot study, it was determined that the sample size would have 80% power with at least 39 people in each group for an effect size of $\alpha=0.05$ and $d=0.641$. The University Ethics Committee gave its approval, (2023-1293), and the study was carried out in accordance with the Declaration of Helsinki. Participants gave informed consent to participate voluntarily before participating in the study.

Patients who met the inclusion criteria were asked to answer the survey face-to-face. Through the questionnaire, patients' age, gender, height, weight, duration of symptoms, affected side, etc., information was recorded. Then, the patients were divided into two groups according to whether they had COVID before LDH surgery. During the clinical follow-up period after LDH surgery,

the recovery process of the patients was evaluated one month later during the follow-up. Patients' pain levels were evaluated with the Visual Analog Scale (VAS), their quality of life with the Short Form-36 Quality of Life Scale (SF-36), their disability levels with the Oswestry Disability Index (ODI), and their anxiety levels with the Beck Anxiety Inventory (BAI).

Data Collection tools

Pain severity

The severity of low back pain the patients experienced during their daily activities was evaluated with VAS. VAS consists of a 0-10 cm line, and the patient is asked to mark their pain level. As the score increases, the pain intensity increases (5).

Quality of life

The patient's quality of life was evaluated using SF-36. SF-36 appraises quality of life across eight domains and 36 items. These domains are physical function, social functioning, body pain, physical limitations, emotional limitations, energy/fatigue, general health perception, and mental health. The scale score ranges from 0 to 100, and an increase in score indicates an increase in quality of life (15).

Disability

ODI was used to evaluate the degree of loss of function that occurred with low back pain. The questionnaire consists of 10 items assessing travel, lifting, carrying, pain intensity, walking, sitting, sleep, degree of pain change, standing, self-care, and social life. Each question is scored between "0" and "5". A higher score indicates more disability (16).

Anxiety

The anxiety level of the patients was evaluated with BAI. The scale is a 21-item self-report scale to measure the severity of self-reported anxiety. It is a Likert-type scale scored between 0-3. The total score varies between 0-64, and as the score increases, the anxiety level also increases (17).

Statistical Analysis

SPSS version 25 software was used in the study to conduct statistical analysis. The normal distribution of variables was examined histograms and Kolmogorov-Smirnov. When comparing normally distributed data, Student's t-test was used, while Mann Whitney-U test was employed for data that did not follow normal distribution. The difference between the two groups in terms of these factors was compared using Chi Square or Fischer tests, depending on the situation. P value below 0.05 were considered statistically significant.

RESULTS

Eighty patients diagnosed with LDH and planned for surgery were included in the study. Forty patients

scheduled for LDH surgery had been diagnosed with COVID-19 in the last six months, and the other 40 patients did not have any symptoms. The patients were evaluated at the 1-month follow-up after surgery and divided into two groups: those with COVID and those without. While the average age of patients with LDH who had COVID was 49.1 ± 12.2 , the average age of patients with COVID (-) was 49.7 ± 12.9 . Sociodemographic information of the groups was similar to each other ($p > 0.05$, Table 1).

It was found that the average physical role, physical function, mental health, body pain and social function

scores on the SF-36 of patients participating in the study are statistically lower in the LDH+ COVID-19 (+) patient group than the participants of the LDH+ COVID-19 (-) patient group (Table 2). According to Table 2 and Figure 1, the study found no statistically significant difference in emotional role, vitality, and mean general health perception scores between the two groups. The consecutive p-values for these variables were 0.296, 0.133, and 0.508, respectively, based on the SF-36. Based on the study, the LDH+ COVID-19 (+) patients had a higher BAI, VAS, and ODI score compared to the LDH+ COVID-19 (-) patients ($p < 0.05$).

Table 1. Evaluation of demographic characteristics of participants according to groups

		Group		p
		LDH+COVID (-)	LDH+COVID (+)	
Sex, n (%)	Female	21 (52.5)	19 (47.5)	0.823
	Male	19 (47.5)	21 (52.5)	
Marital status, n (%)	Married	36 (90)	30 (75)	0.141
	Single	4 (10)	10 (25)	
Dominant hand, n (%)	Right	38 (95)	37 (92.5)	1.000
	Left	2 (5)	3 (7.5)	
Smoking status, n (%)	Smoker	26 (65)	26 (65)	1.000
	Non smoker	14 (35)	14 (35)	
Occupational status, n (%)	Housewife	18 (45)	13 (32.5)	0.415
	Officer	4 (10)	7 (17.5)	
	Employee	16 (40)	15 (37.5)	
	Retired	2 (5)	5 (12.5)	
Educational status, n (%)	Illiterate	1 (1.2)	0 (0)	0.584
	Primary school	14 (35)	11 (12.5)	
	High school	19 (47.5)	19 (47.5)	
	University	6 (15)	10 (25.9)	
Lumbar disc level, n (%)	L1/L2	0 (0)	0 (0)	0.939
	L2/L3	0 (0)	1 (2.5)	
	L3/L4	3 (7.5)	3 (7.5)	
	L4/L5	14 (35)	15 (37.5)	
	L5/S1	23 (57.5)	21 (52.5)	
Chronic diseases, n (%)	None	27 (67.5)	32 (80)	0.233
	Diabetes mellitus	10 (25)	4 (10)	
	Heart disease	0 (0)	1 (2.5)	
	Hypertension	3 (7.5)	3 (7.5)	
	Respiratory diseases	0 (0)	0 (0)	
	Other	0 (0)	0 (0)	
Age, X \pm SD		49.7 \pm 12.9	49.1 \pm 12.2	0.817
Weight (kg), X \pm SD		78.6 \pm 11.8	78 \pm 11.7	0.813
BMI (kg/m ²), X \pm SD		27 \pm 2.9	26.7 \pm 2.4	0.601

BMI: body mass index, SD: standard deviation

Table 2. Comparison of BAI, ODI, VAS and SF-36 subscales between both groups						
	Group	Mean	SD	Min	Max	p
BAI	LDH+COVID (-)	11.5	3.3	7	19	<0.001
	LDH+COVID (+)	16.4	5.9	7	30	
ODI	LDH+COVID (-)	61.5	16.9	28	96	0.003
	LDH+COVID (+)	73.3	16.9	42	100	
VAS	LDH+COVID (-)	4.4	1.5	2	7	0.014
	LDH+COVID (+)	5.3	1.9	2	8	
SF-36						
Role physical	LDH+COVID (-)	8.8	21.6	0	100	0.024
	LDH+COVID (+)	0.6	4	0	25	
Role emotional	LDH+COVID (-)	5	19.3	0	100	0.296
	LDH+COVID (+)	0.8	5.3	0	33.3	
Physical functioning	LDH+COVID (-)	40.4	25.8	0	85	0.003
	LDH+COVID (+)	22.9	19.5	0	55	
Vitality	LDH+COVID (-)	28	10.6	5	45	0.133
	LDH+COVID (+)	24.8	11.4	0	50	
Mental health	LDH+COVID (-)	51.3	5.7	32	64	0.008
	LDH+COVID (+)	47.7	7.2	32	60	
General health	LDH+COVID (-)	40.8	13	15	65	0.508
	LDH+COVID (+)	38.5	15.2	5	65	
Bodily pain	LDH+COVID (-)	40.6	14	10	67.5	<0.001
	LDH+COVID (+)	23.3	18.3	0	55	
Social functioning	LDH+COVID (-)	40.6	14.1	0	62.5	<0.001
	LDH+COVID (+)	27.5	16.3	0	50	

BAI: Beck Anxiety Inventory, ODI: Oswestry Disability Index, VAS: Visual Analog Scale, SF-36: Quality of Life-Short Form, SD: standart deviation, LDH: Lumbar Disc Herniation

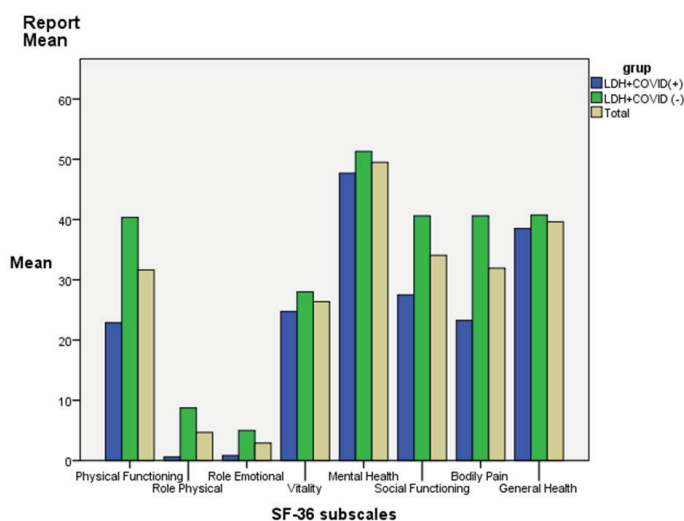


Figure 1. Comparison of the quality of life of LDH Covid-19 (+) and LDH Covid-19 (-) patients. Physical role, physical function, mental health, body pain and social function in the SF-36 quality of life scale of the cases in the LDH + Covid 19 (+) patient group mean score was significantly lower

DISCUSSION

This study determined that disability, anxiety, and pain scores in patients who had LDH surgery and had COVID-19 were significantly higher than in patients without COVID-19. Moreover, the results show that contracting COVID-19 disease plays an important role in the quality of life of patients with LDH.

In addition to common symptoms such as fever, cough, myalgia, and fatigue, musculoskeletal pain can also be an important symptom of COVID-19. Additionally, musculoskeletal disorders associated with COVID-19 may also lead to increased disability in patients (18,19). According to studies, people with COVID-19 infections may experience worsening neck and back pain, which may persist even after the infection is cured (20). Research indicates that during the COVID-19 pandemic, there has been a rise in the prevalence and severity of low back pain in comparison to pre-pandemic levels (18-20). A meta-analysis showed that the intensity of low back pain increased significantly during the COVID-19, and the

decrease in physical activity rate played an important role (21). Present study, similar to the existing literature, it was determined that patients diagnosed with COVID-19 and who underwent LDH surgery had higher pain levels than those who did not have COVID-19. This may have been caused by lifestyle changes, such as a sedentary lifestyle and weight gain, caused by isolation methods taken to reduce the spread of COVID-19 disease.

COVID-19 may lead to radical changes in the living conditions of society due to disease and restrictions, leading to negative physical and psychological consequences (22,23). It has been stated that myalgia is frequently observed in one-quarter of symptomatic COVID-19 patients (24). Anxiety and depression symptoms are more common in patients with low back pain and are thought to be twice as common as in the general population (25). It is also stated that one-third of patients operated on for LDH experience anxiety and depression (26,27). Studies show that anxiety and depression are substantial contributing factors to decreased quality of life in patients undergoing spine surgery (28,29). In this study, it was determined that LDH patients who had COVID-19 had higher anxiety levels than those who did not have COVID-19. When examined, this situation may be due to the permanent symptoms and psychological effects of COVID-19 infection on patients. Therefore, clinicians need to be more careful with LDH patients who have had COVID-19 and have high levels of anxiety in terms of negative surgical outcomes or subsequent maladaptive rehabilitation. Additionally, studies have shown that there is a relationship between preoperative pain, anxiety, and depression (30,31). Inadequate pain management in LDH patients whose psychological risk factors cannot be adequately evaluated may cause chronic pain and lead to increased anxiety and depression.

A person's psychological well-being is negatively impacted, and their quality of life is diminished when they are unable to engage in social and everyday activities due to their illness (32). Previous studies have found that patients with persistent low back pain score lower on quality-of-life measures (33,34). Another study found a correlation between the physical component scores and quality of life in individuals with persistent low back pain (34). In a different study, the quality-of-life scores of one hundred patients with lumbar discopathy who were going to have surgery were shown to be lower than those of healthy volunteers (35). In this study, COVID-19 positive (COVID-19+) LDH patients showed more impairment in their physical role, physical function, mental health, bodily pain, and social function subscale quality of life scores than did COVID-19 negative (COVID-19-) LDH patients. Previous research indicates that COVID-19 has a detrimental impact on patients' quality of life. Furthermore, COVID-19 has been linked to psychological symptoms that impact mental health status, including anxiety, depression, and post-traumatic stress disorder (36). Therefore, the decline in individual functionality brought on by the incapacity to adjust to everyday living activities

and social interactions may account for the decline in quality of life observed in COVID-19+ LDH patients in our investigation. Consequently, it may be said that a lower quality of life is caused by both higher pain and decreased mental health.

The connection between patients with persistent low back pain and their avoidance of pain has garnered attention in recent years (36). Patients with persistent low back pain are more disabled when they suffer from psychosocial variables such as anxiety, sadness, and pain phobia (38,39). Furthermore, a study found a correlation between pain thresholds and disability (40). The association between pain and incapacity can be explained by psychological states, fear, and self-efficacy. The study found that patients with COVID-19 (+) LDH had considerably higher degrees of impairment. The rise in the disability rate has an impact on this scenario because of the rising levels of dread and anxiety during the pandemic.

CONCLUSION

This study found that patients with COVID-19 (+) LDH had higher levels of anxiety, pain, and disability and poorer quality of life compared to patients without COVID-19. Clinicians must understand the role of social stresses created by pandemic situations such as COVID-19 on quality of life and healthcare utilization. Therefore, the relationship of psychosocial factors with COVID-19 should be considered during the clinical follow-up and rehabilitation process after surgery.

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REFERENCES

1. Amin RM, Andrade NS, Neuman BJ. Lumbar disc herniation. *Curr Rev Musculoskelet Med.* 2017;10:507-16.
2. Somma F, Negro A, D'Agostino V, et al. COVID-19 and low back pain: previous infections lengthen recovery time after intradiscal ozone therapy in patients with herniated lumbar disc. *Radiol Med.* 2022;127:673-80.
3. Deyo RA, Mirza SK. CLINICAL PRACTICE. Herniated lumbar intervertebral disk. *N Engl J Med.* 2016;374:1763-72.
4. Sarı S, Aydoğan M. Bel ağrısının önemli bir sebebi: lomber disk hernisi. *Totbid Dergisi.* 2015;14:298-304.
5. Murphy K, Muto M, Steppan J, et al. Treatment of contained herniated lumbar discs with ozone and corticosteroid: a pilot clinical study. *Can Assoc Radiol J.* 2015;66:377-84.
6. Miyoshi S, Sekiguchi M, Konno S, et al. Increased expression of vascular endothelial growth factor protein in dorsal root ganglion exposed to nucleus pulposus on the nerve root in rats. *Spine (Phila Pa 1976).* 2011;36:E1-6.

7. Giurazza F, Guarnieri G, Murphy KJ, Muto M. Intradiscal O₂O₃: rationale, injection technique, short- and long-term outcomes for the treatment of low back pain due to disc herniation. *Can Assoc Radiol J*. 2017;68:171-7.
8. Smith BJ, Lim MH. How the COVID-19 pandemic is focusing attention on loneliness and social isolation. *Public Health Res Pract*. 2020;30:3022008.
9. Killgore WDS, Cloonan SA, Taylor EC, Dailey NS. Loneliness: a signature mental health concern in the era of COVID-19. *Psychiatry Res*. 2020;290:113117.
10. Karayannis NV, Baumann I, Sturgeon JA, Melloh M, Mackey SC. The impact of social isolation on pain interference: a longitudinal study. *Ann Behav Med*. 2019;53:65-74.
11. Karos K, McParland JL, Bunzli S, et al. The social threats of COVID-19 for people with chronic pain. *Pain*. 2020;161:2229-35.
12. Chaturvedi SK. Health anxiety, health-related life events, and somatization during COVID-19 pandemic can increase chronic pain. *Pain*. 2020;161:2652.
13. Nandasena HMRKG, Pathirathna ML, Atapattu AMMP, Prasanga PTS. Quality of life of COVID 19 patients after discharge: systematic review. *PLoS One*. 2022;17:e0263941.
14. Ferreira LN, Pereira LN, da Fé Brás M, Ilchuk K. Quality of life under the COVID-19 quarantine. *Qual Life Res*. 2021;30:1389-405.
15. Ware JE Jr. SF-36 health survey update. *Spine (Phila Pa 1976)*. 2000;25:3130-9.
16. Fairbank JC, Pynsent PB. The Oswestry disability index. *Spine (Phila Pa 1976)*. 2000;25:2940-52.
17. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol*. 1988;56:893-7.
18. Şahin T, Ayyıldız A, Gencer-Atalay K, et al. Pain Symptoms in COVID-19. *Am J Phys Med Rehabil*. 2021;100:307-12.
19. Bailly F, Genevay S, Foltz V, et al. Effects of COVID-19 lockdown on low back pain intensity in chronic low back pain patients: results of the multicenter CONFILOMB study. *Eur Spine J*. 2022;31:159-66.
20. San AU, Kesikburun S, Tezel K. The effect of social isolation during the COVID-19 pandemic on patients with chronic low back pain who underwent a spine intervention. *Pain Physician*. 2021;24:319-25.
21. Papalia GF, Petrucci G, Russo F, et al. COVID-19 pandemic increases the impact of low back pain: a systematic review and meta-analysis. *Int J Environ Res Public Health*. 2022;19:4599.
22. Wang C, Pan R, Wan X, et al. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. *Int J Environ Res Public Health*. 2020;17:1729.
23. Erdogdu Y, Koçoğlu F, Sevim C. An investigation of the psychosocial and demographic determinants of anxiety and hopelessness during COVID-19 pandemic. *J Clin Psy*. 2020;23:24-37.
24. Öztürk O, Özer Kaya D. Effect of COVID-19 on musculoskeletal system. *İKÇÜSBFD*. 2020;5:179-82.
25. Moore JE. Chronic low back pain and psychosocial issues. *Phys Med Rehabil Clin N Am*. 2010;21:801-15.
26. Arts MP, Kols NI, Onderwater SM, Peul WC. Clinical outcome of instrumented fusion for the treatment of failed back surgery syndrome: a case series of 100 patients. *Acta Neurochir (Wien)*. 2012;154:1213-7.
27. Falavigna A, Righesso O, Teles AR, et al. Depression subscale of the hospital anxiety and depression scale applied preoperatively in spinal surgery. *Arq Neuropsiquiatr*. 2012;70:352-6.
28. Celestin J, Edwards RR, Jamison RN. Pretreatment psychosocial variables as predictors of outcomes following lumbar surgery and spinal cord stimulation: a systematic review and literature synthesis. *Pain Med*. 2009;10:639-53.
29. Abbott AD, Tyni-Lenné R, Hedlund R. Leg pain and psychological variables predict outcome 2-3 years after lumbar fusion surgery. *Eur Spine J*. 2011;20:1626-34.
30. Strøm J, Bjerrum MB, Nielsen CV, et al. Anxiety and depression in spine surgery—a systematic integrative review. *Spine J*. 2018;18:1272-85.
31. Dunn LK, Durieux ME, Fernández LG, et al. Influence of catastrophizing, anxiety, and depression on in-hospital opioid consumption, pain, and quality of recovery after adult spine surgery. *J Neurosurg Spine*. 2018;28:119-26.
32. Dündar Ü, Solak Ö, Demirdal ÜS, et al. Kronik bel ağrılı hastalarda ağrı, yeti yitimi ve depresyonun yaşam kalitesi ile ilişkisi. *Genel Tıp Dergisi*. 2019;19:99-104.
33. Keeley P, Creed F, Tomenson B, et al. Psychosocial predictors of health-related quality of life and health service utilisation in people with chronic low back pain. *Pain*. 2008;135:142-50.
34. Agnus Tom A, Rajkumar E, John R, Joshua George A. Determinants of quality of life in individuals with chronic low back pain: a systematic review. *Health Psychol Behav Med*. 2022;10:124-44.
35. Veresciagina K, Ambrozaitis KV, Spakauskas B. Health-related quality-of-life assessment in patients with low back pain using SF-36 questionnaire. *Medicina (Kaunas)*. 2007;43:607-13.
36. Shanbehzadeh S, Tavahomi M, Zanjari N, et al. Physical and mental health complications post-COVID-19: scoping review. *J Psychosom Res*. 2021;147:110525.
37. Malik P, Patel K, Pinto C, et al. Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)—A systematic review and meta-analysis. *J Med Virol*. 2022;94:253-62.
38. Nagarajan M, Nair MR. Importance of fear-avoidance behavior in chronic non-specific low back pain. *J Back Musculoskelet Rehabil*. 2010;23:87-95.
39. Kim TS, Pae CU, Hong CK, et al. Interrelationships among pain, disability, and psychological factors in young Korean conscripts with lumbar disc herniation. *Mil Med*. 2006;171:1113-6.
40. Lee H, Hübscher M, Moseley GL, et al. How does pain lead to disability? A systematic review and meta-analysis of mediation studies in people with back and neck pain. *Pain*. 2015;156:988-97.



Retrospective Analysis of Injuries Resulting from Traffic Accidents

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Abstract

Aim: To evaluate injuries and organ damage occurring in traffic accidents, and the cause of death in cases with mortality.

Material and Method: The study included cases involved in traffic accidents who presented at hospital in a 4-year period. The cases were evaluated in respect of age, gender, injuries, alcohol consumption, form of involvement in traffic, and cause of death in deceased cases. The data were analyzed using SPSS vn. 26.0 software.

Results: The total 3039 cases included in the study comprised 68.08% males and 31.92% females. Of the cases who presented at hospital, 4.11% died. The age group most involved in accidents was the 20-29 years group. The bones most frequently fractured were the costae. According to body regions, the nasal bone was the bone most often fractured in the head region, the humerus in the upper extremities, the pubis in the pelvis, the tibia in the lower extremities, and the costae in the chest region. The abdominal organ most often damaged was the liver.

Conclusion: A statistically significant correlation was determined between gender and fractures of the ischium, sacrum, iliac, and pubic bones, with these fractures seen more in females than males. This higher rate of pelvic fractures in females can be attributed to the differences in male and female pelvic anatomy.

Keywords: Traffic accidents, injuries, death

INTRODUCTION

Traffic accidents have started to become a significant health problem both in Türkiye and throughout the world. According to World Health Organization (WHO) data, there are approximately 1.19 million deaths per year as a result of traffic accidents, more than 20-50 million individuals are injured, and most of these injuries result in disability (1).

Traffic accidents cause significant economic losses for both individuals and society. According to WHO data, road traffic accidents constitute a cost of 3% of gross domestic product of many countries (1). These losses are due to not only treatment costs, but also the loss of productivity of family members requiring leave of absence from work or school to care for those who are injured or disabled, and of those who die because of their injuries. Due to the increased number of vehicles with the economic development of countries, there has been an increase in the number of traffic accidents and deaths related to traffic accidents (2). One of the most frequent causes of early death throughout the world is traffic accidents (3).

Injuries sustained in road traffic accidents are the leading cause of death for children and young adults aged 5-29 years (1). Traffic accidents are ranked 12th in the causes leading to death worldwide (4).

Together with developing technology, transport options have increased both in Türkiye and throughout the world. Although the options have increased, road transport is generally predominant worldwide, and this is the case in Türkiye (5).

The aim of this study was to determine injuries and organ damage occurring in traffic accidents, and the cause of death in cases with mortality.

MATERIAL AND METHOD

Approval for the study was granted by the Health Sciences Non-Interventional Clinical Research Ethics Committee of İnönü University (Decision no: 2021/2763, Session no: 24, Dated: 30.11.2021). Data of the cases included in the study were retrieved from the ward notes, consultation notes, radiological images, radiological results, laboratory tests,

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epicrisis notes, and the records of polyclinic follow-up examinations in the hospital automated records system.

The patients involved in traffic accidents were evaluated in respect of age, gender, injuries, cause of death, alcohol consumption, and type of traffic accident. The patients were separated into age groups, as 0-9 years (0=birth to 12 months), 10-19 years, 20-29 years, and in decades thereafter.

The type of traffic accident was defined as unknown, within vehicle-driver, within vehicle -passenger, within vehicle-unknown whether driver or passenger, not in a motor vehicle (pedestrian, cyclist), motorcycle, tractor, other agricultural vehicles, train. Traffic accidents experienced by individuals within cars, buses, minibuses, lorries, pickup trucks, articulated lorries, and tow trucks, were accepted as "within vehicle traffic accident".

Statistical Analysis

Data obtained in the study were analyzed statistically using IBM SPSS Statistics vn. 26.0 software. In the analyses of the data, the Pearson Chi-square test, and Yates corrected Chi-square test were used. A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

Within the defined study period, a total of 3039 individuals were involved in traffic accidents. The most presentations at hospital because of a traffic accident were seen to be in 2020 (Table 1).

Table 1. Number of traffic accidents per year

Year	n (%)
2017	764 (25.1)
2018	723 (23.8)
2019	758 (24.9)
2020	794 (26.1)
Total	3039 (100)

The type of traffic accident seen most frequently was within-vehicle traffic accident and train accidents were seen the least often. As the province of Malatya is an agricultural area, there were also accidents involving tractors and other agricultural vehicles (Table 2).

Table 2. Types of traffic accidents in which the cases were involved

Type of traffic accident	n (%)
Unknown	182 (5.99)
Within vehicle-unknown whether driver or passenger	1783 (58.67)
Within vehicle-driver	128 (4.21)
Within vehicle-passenger	138 (4.54)
Not a motor vehicle (pedestrian, bicycle)	427 (14.05)
Motorcycle	188 (6.19)
Tractor	110 (3.62)
Other agricultural vehicle	78 (2.57)
Train	5 (0.16)
Total	3039 (100)

The total cases comprised 68.08% males and 31.92% females. The mean age was determined to be 33.806 ± 19.447 years, median age was 31 years, and the age range was from 0 to 95 years. The age group most involved in traffic accidents was determined to be the 20-29 years age group, followed by the 30-39 years group (Table 3).

Table 3. Distribution of traffic accident cases according to gender and age groups

		n (%)
Gender	Male	2069 (68.08)
	Female	970 (31.92)
Age groups (years)	0-9	306 (10.07)
	10-19	469 (15.43)
	20-29	679 (22.34)
	30-39	514 (16.91)
	40-49	406 (13.36)
	50-59	287 (9.44)
	60-69	227 (7.47)
	70-79	120 (3.95)
	80-89	28 (0.92)
90-99	3 (0.10)	

Alcohol was determined to be present in 152 (5%) cases. As there were cases of unknown type of accident, the rate of drivers who had consumed alcohol could not be clearly determined. Mortality developed in 125 (4.11%) of the traffic accident cases. The cause of death was determined by examining the data in the hospital information system (clinician notes, radiological imaging results, etc.). For the cases where the cause of death could not be explained from the hospital data, the autopsy reports had to be examined, but as the forensic autopsies were conducted in a different centre, the autopsy reports could not be accessed. Of the exitus cases, the cause of death was skull fracture together with intracranial bleeding in 14.4%, and in 30.4% of cases, the cause of death could not be determined (Table 4).

Table 4. Cause of death in traffic accident cases

Cause of death	n (%)
No death	2914 (95.89)
Cause of death undetermined	38 (1.25)
Skull fracture together with intracranial bleeding	18 (0.59)
Only internal organ damage	18 (0.59)
Internal organ damage together with intracranial bleeding	16 (0.53)
Internal organ damage, skull fracture, and intracranial bleeding	15 (0.49)
Only intracranial bleeding	8 (0.26)
Only skull fracture	5 (0.16)
Internal organ damage together with major vascular injuries	3 (0.10)
Internal organ damage and skull fracture	2 (0.07)
Medulla spinalis injury together with skull fracture	1 (0.03)
Only major vascular injuries	1 (0.03)

The bones most frequently fractured were determined to be costae at the rate of 12.08%, followed by vertebrae at 10.86%, and the nasal bone at 4.74%. The bone most often fractured in the head region was determined to be the nasal bone. In the other regions of the body, the most frequently

fractured bones were seen to be the humerus (3.29%) in the upper extremities, the pubis (3.92%) in the pelvis, the costae (12.08%) in the chest region, and the tibia (4.74%) in the lower extremities. The liver was determined to be the abdominal organ most often damaged (2.40%) (Table 5).

Table 5. Injuries resulting from traffic accidents			
Injury type	n (%)	Injury type	n (%)
Nasal fracture	144 (4.74)	Humerus fracture	100 (3.29)
Subarachnoid bleeding	141 (4.64)	Radius fracture	98 (3.22)
Frontal fracture	97 (3.19)	Ulna fracture	56 (1.84)
Subdural bleeding	96 (3.16)	Metacarpal fracture	28 (0.92)
Temporal fracture	86 (2.83)	Hand phalanx fracture	26 (0.86)
Maxilla fracture	79 (2.60)	Carpal bone fracture	16 (0.53)
Orbita fracture	72 (2.37)	Shoulder dislocation	8 (0.26)
Cerebral contusion	69 (2.27)	Elbow dislocation	2 (0.07)
Zygoma fracture	62 (2.04)	Pubis fracture	119 (3.92)
Epidural bleeding	57 (1.88)	Acetabulum fracture	78 (2.57)
Occipital fracture	46 (1.51)	Sacrum fracture	58 (1.91)
Parietal fracture	45 (1.48)	Iliac fracture	51 (1.68)
Mandibula fracture	40 (1.32)	Ischium fracture	46 (1.51)
Sphenoid fracture	34 (1.12)	Sacroiliac separation	24 (0.79)
Ethmoid fracture	32 (1.05)	Hip dislocation	19 (0.63)
Pneumocephaly	27 (0.89)	Pubic diastasis	9 (0.30)
Cerebral parenchyma bleeding or hematoma	22 (0.72)	Tibia fracture	144 (4.74)
Diffuse axonal damage	18 (0.59)	Femur fracture	137 (4.51)
Cornea laceration	12 (0.39)	Fibula fracture	113 (3.72)
Ventricular bleeding	6 (0.20)	Tarsal bone fracture	37 (1.22)
Septum fracture	6 (0.20)	Patella fracture	31 (1.02)
Sclera laceration	2 (0.07)	Metatarsal fracture	28 (0.92)
Cerebellar bleeding-hematoma	2 (0.07)	Foot phalanx fracture	10 (0.33)
Costae fracture	367 (12.08)	Liver laceration or hematoma	73 (2.40)
Lung contusion	190 (6.25)	Spleen laceration or hematoma	46 (1.51)
Pneumothorax	177 (5.82)	Kidney laceration or hematoma	21 (0.69)
Clavicle fracture	126 (4.15)	Renal gland bleeding or hematoma	4 (0.13)
Hemothorax	91 (2.99)	Stomach or intestine perforation	4 (0.13)
Scapula fracture	91 (2.99)	Bladder rupture	2 (0.07)
Sternum fracture	45 (1.48)	Testis injury	2 (0.07)
Traumatic cyst in the lung	15 (0.49)	Pancreas laceration	2 (0.07)
Acromioclavicular dislocation-separation	7 (0.23)	Placenta detachment	1 (0.03)
Diaphragm rupture	1 (0.03)	Urethra rupture	1 (0.03)
Mitral papillary muscle rupture	1 (0.03)	Ureter rupture	1 (0.03)
Vertebra fracture or dislocation	330 (10.86)	Nerve damage	22 (0.72)
Spinal cord injury	6 (0.19)	Compartment syndrome	2 (0.07)
Tendon rupture	43 (1.41)	Major vascular injury	27 (0.89)

Costae fractures were seen most in males, and vertebrae fracture/dislocation in females. A significant correlation was determined between ischium, sacrum, iliac, and pubic fractures and gender, with these fractures seen more

in females than in males. A significant correlation was determined between costa, zygoma, and scapula fractures and gender with these fractures seen more in males than in females (Table 6).

Table 6. Distribution of injuries according to gender

		Gender		p value
		Male n (%)	Female n (%)	
Ischium fracture	Absent	2050 (99.08)	943 (97.22)	<0.001**
	Present	19 (0.92)	27 (2.78)	
Sacrum fracture	Absent	2043 (98.74)	938 (96.70)	<0.001*
	Present	26 (1.26)	32 (3.30)	
Iliac fracture	Absent	2042 (98.70)	946 (97.53)	0.029**
	Present	27 (1.30)	24 (2.47)	
Pubic fracture	Absent	2012 (97.25)	908 (93.61)	<0.001*
	Present	57 (2.75)	62 (6.39)	
Costa fracture	Absent	1799 (86.95)	873 (90.00)	0.016*
	Present	270 (13.05)	97 (10.00)	
Scapula fracture	Absent	1996 (96.47)	952 (98.14)	0.016**
	Present	73 (3.53)	18 (1.86)	
Zygoma fracture	Absent	2019 (97.58)	958 (98.76)	0.045**
	Present	50 (2.42)	12 (1.24)	
Vertebra fracture and dislocation	Absent	1844 (89.13)	865 (89.18)	0.967*
	Present	225 (10.87)	105 (10.82)	

*: Pearson Chi-square test, **: Yates corrected chi-square test

DISCUSSION

The gender distribution of the traffic accident cases in this study was found to be 68.08% males and 31.92% females. In a study in Sri Lanka by Fernando et al., the rate of males was 72% and females was 28% (6). Gender distribution in other studies has been determined to be males 69.7% and females 30.3% by Varlik et al. (7), 68.2% males and 31.8% females by Perysinakis et al. in a study in Crete (8), 71.2% males and 28.8% females by Kourouma et al. in a study in Guinea (9), and 69% males and 31% females by Özdemir et al. in a study in İstanbul (10). The current study rates were seen to be consistent with those of previous studies.

The mean age of the traffic accident cases in the current study was 33.806±19.447 years and the median age was 31 years. Previous studies in Türkiye have reported these ages as mean 35.33±18.26 years and median 32 years by Polat in a study in Edirne (11), 32.06 years by Özdemir et al. in İstanbul (12), mean 30.57±18.44 years by Varol et al. in Sivas (13), and mean 35 years by Çetinoğlu et al. in Samsun (14). The mean age of the cases in the current study was seen to be consistent with these previous studies.

In the current study, the age group that presented most often at hospital was the 20-29 years age group (22.34%), followed by the 30-39 years group (16.91%). In a study in İzmir, Bilgin et al. reported that the 21-25 years age group (13.4%) was most frequently involved in traffic accidents,

followed by the 26-30 years age group, and in total the 21-30 years group was involved in traffic accidents at the rate of 26.3% (15). Özdemir et al. determined traffic accident cases in the 19-35 years age group at the rate of 44.2% in İstanbul (10). In a study in Tokat by Armağan et al., there was seen to be a peak in patients in the age range of 20-30 years (16). The current study results on this point were consistent with the findings in literature. The greater involvement of the young population in traffic accidents can be attributed to a more active social life, more travelling, and using more exciting and fast cars.

The types of accidents in the current study were found to be within vehicle traffic accidents at the rate of 67.42%, outside the vehicle at 14.5%, motorcycle accidents at 6.19%, tractor accidents at 3.62%, and other agricultural vehicle accidents at 2.57%. In a study in Edirne, Polat et al. reported rates of 55.5% for within vehicle accident cases and 44.5% for outside the vehicle (11). Bilgin et al. reported 48.6% within vehicle accidents and 46.3% outside the vehicle in a study in İzmir (15). In a study in Ankara, Durdu et al. determined that most traffic accidents were within vehicle accidents followed by outside the vehicle, and motorcycles (17). Özdemir et al. in İstanbul stated rates of 51.4% within vehicle accidents, 29.5% outside the vehicle, 16.6% motorcycles, 1.9% bicycles, and 0.6% horse-drawn vehicles (10). The rate of within vehicle traffic accidents in the current study was higher than the rates reported in

these other studies.

The current study results showed that ischium, sacrum, iliac, and pubic fractures occurred more in females than in males. Compared to males, the pelvic bones of females are thinner, the attachment sites of muscles and ligaments are less evident, the spina iliaca anterior superior are further from each other and the apertura pelvis superior is round in shape and wider (18). That there were more ischium, sacrum, iliac, and pubic fractures in females was thought to be due to the difference in pelvis anatomy.

In the current study, the costae were the bones most frequently fractured, followed by vertebrae fracture/dislocation. When evaluated according to body regions, the most frequently fractured bones were seen to be the humerus in the upper extremities, the pubis in the pelvis, and the tibia in the lower extremities. In males the most frequently fractured bones were the costae, and in females vertebrae fracture/dislocation. When traffic accidents were evaluated in general by Polat et al. in a study in Edirne, the most frequently fractured bones were determined to be the costae, followed by vertebrae (11). In another study by Aloudah et al. in Saudi Arabia of patients hospitalised because of of bone fracture following a traffic accident, the femur was seen to be the most frequently fractured bone, followed by the humerus, and vertebrae. In males, the femur was fractured most often and in females, the humerus (19). In a study in Nigeria by Igbo et al., of the bones fractured after a traffic accident, the femur was seen to be the most frequent followed by the tibia/fibula (20). The results of the current study were seen to be consistent with the findings of some studies and different from those of some others.

CONCLUSION

Traffic accidents are a preventable health problem. To be able to decrease the number of traffic accidents, more importance must be given to traffic education, practical examinations should be longer and more difficult, and the driving ability of individuals should be sufficiently supervised. For drivers, passengers, and pedestrians to follow the rules of the road, traffic penalties should be increased to an amount that will be a deterrent.

A significant correlation was determined between ischium, sacrum, iliac, and pubic fractures and gender, with these fractures seen more in females than in males. That there were more pelvic fractures in females was thought to be due to the difference in pelvis anatomy.

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REFERENCES

1. World Health Organization. Road traffic injuries. <https://www.who.int/news-room/fact-sheets/detail/road-traffic-injuries> access date 06.04.2024.
2. Sharma BR, Harish D, Sharma V, Vij K. Road-traffic accidents-a demographic and topographic analysis. *Med Sci Law*. 2001;41:266-74.
3. Rehm J, Room R, Monteiro M, et al. Alcohol use. In: Ezzati M, Lopez AD, Rodgers A, Murray CJL, eds. *Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors*. Vol 1. World Health Organization; 2004:959-1108.
4. World Health Organization. *Global Status Report on Road Safety 2023*, Section 1;4.
5. Doğan Z, Dikmen BB. Comparison of Transportation Sector and Types of Transportation in Turkey. *Journal of International Social Research*. 2018;11:758-70.
6. Fernando DM, Tennakoon SU, Samaranayake AN, Wickramasinghe M. Characteristics of road traffic accident casualties admitted to a tertiary care hospital in Sri Lanka. *Forensic Sci Med Pathol*. 2017;13:44-51.
7. Varlık M, Eroğlu SE, Özdemir S, et al. Araç içi trafik kazası ile acil servisine başvuran hastaların değerlendirilmesi. *Fırat Tıp Dergisi*. 2019;24:186-92.
8. Perysinakis I, Spartinou A, Siligardou MR, et al. Pattern of road traffic injuries in the Rethymnon region, Crete, Greece: a secondary hospital-based study. *Rural Remote Health*. 2021;21:6529.
9. Kourouma K, Delamou A, Lamah L, et al. Frequency, characteristics and hospital outcomes of road traffic accidents and their victims in Guinea: a three-year retrospective study from 2015 to 2017. *BMC Public Health*. 2019;19:1022.
10. Özdemir M, Naziroğlu A, Yıldız AM, Inancı MA. Forensic medical evaluation of cases admitted to the emergency department of a training and research hospital as a result of traffic accident, based on clinical records. *Turkish Journal of Forensic Medicine*. 2021;35:44-53.
11. Polat MÖ. 2017-2019 Yılları Arasında Trakya Üniversitesi Hastanesi acil servisine başvuran trafik kazası olgularının adli tıp açısından değerlendirilmesi. Master thesis. Trakya University, Edirne, 2020.
12. Özdemir S, Akoğlu EÜ, Baykal T. Evaluation of demographic and clinical characteristics of patients presenting to the emergency department with traffic accidents. *Boğaziçi Tıp Dergisi*. 2016;3:85-9.
13. Varol O, Eren ŞH, Oğuztürk H, et al. Investigation of the patients who admitted after traffic accident to the emergency department C. Ü. Tıp Fakültesi Dergisi. 2006;28:55-60.
14. Çetinoğlu EÇ, Canbaz S, Tomak L, Pekşen Y. Evaluation of road traffic crashes among admittances to 112 emergency healthcare services in Samsun 2004. *Turk J Emerg Med*. 2007;7:1-4.
15. Bilgin UE, Meral O, Koçak A, et al. Legal examination of the patients admitted to the Emergency Service of Ege University Hospital due to traffic accidents in 2011. *Ege Journal of Medicine*. 2013;52:93-9.

16. Armağan HH, Tomruk Ö, Armağan İ, et al. A retrospective study on cases of accidents inside the vehicle applied to an emergency service of a university hospital. *Gaziosmanpaşa Üniversitesi Tıp Fakültesi Dergisi*. 2013;5:145-52.
17. Durdu T, Kavalcı C, Yılmaz F, et al. Analysis of trauma cases admitted to the emergency department. *Journal of Clinical and Analytical Medicine*. 2014;5:182-5.
18. Oğuz B, Desdicioğlu K. Morphology, radiology and clinical anatomy of pelvis. *Turkish Journal of Health Research*. 2021;2:57-72.
19. Aloudah AA, Almesned FA, Alkanan AA, Alharbi T. Pattern of fractures among road traffic accident victims requiring hospitalization: single-institution experience in Saudi Arabia. *Cureus*. 2020;12:e6550.
20. Igho O, Isaac O, Eronimeh O. Road traffic accidents and bone fractures in Ughelli, Nigeria. *IOSR Journal of Dental and Medical Sciences*. 2015;14:21-5.



Volumetric Evaluation of Substantia Nigra in Major Depressive Disorder Using Atlas-Based Method

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Abstract

Aim: The substantia nigra pars compacta (SNc), a vital part of the brain that produces dopamine, is being closely studied due to its potential role in the monoamine hypothesis, which aims to explain the causes of Major Depressive Disorder (MDD). Dopamine, a chemical messenger in the brain, is linked to the monoamine hypothesis, suggesting that imbalances in these chemicals may contribute to MDD. This study aimed to calculate volumetric changes in the substantia nigra (SN), using brain magnetic resonance imaging (MRI) in individuals diagnosed with MDD.

Material and Method: Sixty-six participants, comprising 33 individuals diagnosed with MDD (mean age=44.30±13.98 years) and 33 healthy individuals (mean age=46.27±14.94 years), were recruited from the university hospital psychiatry outpatient clinic. In the MDD group, there were 15 male participants (45%) and 18 female participants (55%). The healthy control group consisted of 28 males (84.8%) and 5 females (16.2%). Potential confounding factors, such as underlying chronic diseases, were ruled out by the clinician through a thorough examination of the patient's medical history, ensuring the study outcomes were not influenced. Three-dimensional brain MRI scans were conducted using a 1.5 Tesla MRI scanner. Volumes of the SN and midbrain were automatically computed using MRISudio, an atlas-based image analysis program.

Results: Statistically significant higher volumes were observed in the right SN in the MDD group compared to controls (0.146±0.045 cm³ vs. 0.122±0.035 cm³, p=0.02, p<0.05). The ratio of SN to midbrain volume was higher in MDD patients on both sides, with a 22.4% higher value on the right side and a 12.7% higher on the left side relative to controls (p=0.002 for the right, p=0.01 for the left; p<0.05). Moreover, a negative correlation between left and right SN volumes and age was identified in the MDD group (p=0.01 for the left, p=0.05 for the right side; p<0.05).

Conclusion: Our study revealed an increase in SN volume in MDD patients. Identifying volumetric discrepancies in brain regions responsible for dopamine release could hold significant value in elucidating the underlying causes of the disease and guiding treatment strategies.

Keywords: Dopamine, magnetic resonance imaging, major depressive disorder, substantia nigra

INTRODUCTION

Major Depressive Disorder (MDD) has emerged as a pervasive public health issue, severely compromising overall well-being worldwide (1). Global estimates from the 2017 World Health Organization (WHO) report indicate that MDD affects over 300 million individuals, with suicide attempts being a leading cause of mortality, accounting for approximately 800,000 deaths each year (2). MDD's impact on public health surpasses that of other prevalent conditions such as coronary heart disease, rheumatoid arthritis, and diabetes mellitus (3). A study reports a 12-month prevalence of 6.6% and a lifetime prevalence

of 16.2% for MDD (4). Given its significant prevalence and detrimental effects, effective MDD treatment is of paramount importance for public health. A more comprehensive understanding of MDD's pathophysiology and associated morphological changes can significantly enhance diagnosis and treatment strategies in clinical practice (5). Therefore identifying structural findings associated with the monoamine hypothesis, a widely accepted theory regarding MDD's pathophysiology, is crucial (6).

The monoamine hypothesis proposes that a central neurophysiological factor contributing to MDD is a

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reduction in the levels of monoaminergic transmission (serotonin, norepinephrine, and/or dopamine) within the central nervous system (6). Based on this hypothesis, antidepressants, particularly monoamine reuptake inhibitors, have been developed and are extensively used in clinical practice (7). Despite extensive research efforts, direct evidence supporting the monoamine hypothesis remains largely inconclusive (8). Therefore, further research is needed to strengthen the evidence supporting the monoamine hypothesis.

Dopamine, one of the monoamine neurotransmitters, plays a crucial role in various functions of the central nervous system, including regulation of movement, cognitive executive functions, and emotional limbic activity (9). Alterations in dopaminergic pathways have been shown to affect both locomotor activity and cognitive functions (10,11). The midbrain houses approximately 90% of the brain's dopamine-producing neurons. Within the midbrain, the substantia nigra pars compacta (SNc) and ventral tegmental area host the majority of these dopaminergic neurons (12). The SNc, recognized as a dopaminergic nucleus essential for modulating motor movements and reward functions within the basal ganglia circuitry, plays a pivotal role (9).

A study reported an instance in which erroneous deep brain stimulation of the SN resulted in a reversible severe depressive episode (13). Numerous studies have demonstrated a correlation between volumetric changes in the SN observed in various neuropsychiatric disorders and brain functions (14,15).

In our study, we aimed to evaluate substantia nigra (SN) volume differences in MDD patients using brain magnetic resonance imaging (MRI) and an atlas-based automated volumetric measurement method. We believe that assessing volumetric differences in the SN, a critical center for dopamine synthesis, will contribute to elucidating the etiology of MDD.

MATERIAL AND METHOD

Participants

Sixty-six participants were enrolled in our study, including 33 patients diagnosed with MDD (mean age=44.30±13.98 years) and 33 healthy individuals (mean age=46.27±14.94 years), who were recruited from the university hospital psychiatry outpatient clinic. The study comprised 15 male participants (45%) and 18 female participants (55%) in MDD group. 28 males (84.8%) and 5 females (16.2%) were included in healthy control group. No gender-specific analyses were conducted due to asymmetric sex ratios in the study groups. All participants underwent assessment using the Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A).

The clinical assessments in this study were conducted following the guidelines outlined by the American Psychiatric Association (APA) clinical practice guidelines. Participants underwent clinical psychiatric assessment

were subsequently categorized into two groups: a control group comprising individuals with no diagnosed mental health conditions, and a patient group consisting of individuals diagnosed with MDD.

Inclusion criteria for MDD patients were the ability to use their right hand, the absence of any chronic illnesses, and no history of bipolar disorder, psychosis, or other psychiatric disorders in the patient or their first-degree relatives. Exclusion criteria for the healthy control group included a history of any psychiatric disorders, any neurological diseases, a cerebral trauma history resulting in a coma lasting more than five minutes, left-handedness, and the presence of individuals with psychotic or bipolar disorders among their first-degree relatives. No exclusions were made from the healthy group; all participants initially categorized as healthy remained part of the analysis throughout the study.

Ethical approval for this study was obtained from Çanakkale 18 Mart University Ethical Committee (Approval No: 2013/75, dated 09/10/2013), and written informed consent was obtained from all participants.

MRI Protocol

MRI scans were acquired using a 1.5 Tesla Magnetic Resonance unit (Philips Ingenia, Netherlands, 2013). For volumetric measurements, we utilized images acquired in the axial plane using a T1-weighted 3D multiplanar turbo spin-echo sequence. The imaging parameters included voxel dimensions of 1x1x1 mm, a Repetition Time (TR): of 7.0 ms, an Echo Time (TE): of 3.4 ms, a Field of View (FoV): of 256x240, a Matrix: of 256x216, a slice thickness of 0.9 mm, and no gap.

Volumetric Calculation with Atlas-Based Method

The volume of relevant brain structures was automatically calculated using MRISudio, an atlas-based image analysis software developed by H. Jiang and S. Mori at Johns Hopkins University (16). The MRISudio program consists of DTISudio, DiffeoMap, and ROIEditor software. Images were processed using DTISudio and MRICro to separate bone structures. DiffeoMap aligned images with a template, and the subject image was saved as "updated_maskT1." The resulting data were sent for analysis. Each participant's image was linearly and nonlinearly transformed using large deformation diffeomorphic metric mapping to match single-participant skull-stripped templates produced by Johns Hopkins University (17). The DiffeoMap software aligned the template image ("Updated_maskT1") and the subject image ("JHU_MNI_SS_BPM_Typell_V2.1"). The ROIEditor program obtained volumes by overlaying "Updated_Lddmmpposthmap.img0" onto MaskT1, with results saved as "roi statistics" in the working file. After normalizing the MR images, the ROIEditor software was employed to automatically divide the brain into 160-180 anatomical structures and calculate their volumes (Figure 1). Procedures for calculating the volumes of brain regions using MRISudio have been previously described in other studies (16,18).

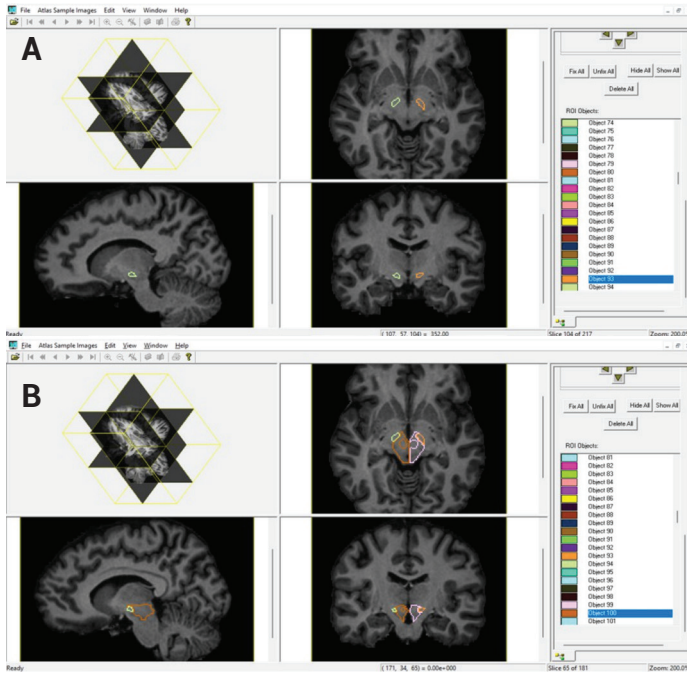


Figure 1. A. Identification of the substantia nigra on normalized images using ROIEditor, B. Identification of the midbrain areas on normalized images using ROIEditor

Statistical Analysis

All volumetric data were expressed as mean±standard deviation (SD). The Shapiro-Wilk test was used for normality analysis of continuous variables. Since continuous variables met the assumption of normality, independent samples t-tests were used in univariate analyses. Similarly, Pearson correlation analysis was used in correlation analyses as continuous variables met the assumption of normality. Results with a p-value less than 0.05 were considered statistically significant.

RESULTS

Sociodemographic data for both the patient and control groups are summarized in Table 1. Volumetric data for the assessed brain structures are presented in Table 2. Patients with MDD exhibited significantly higher right SN volume ($0.146\pm 0.045\text{ cm}^3$ vs. $0.122\pm 0.035\text{ cm}^3$, $p=0.02$, $p<0.05$) (Figure 2), HAM-D, and HAM-A scores compared to the control group ($p=0.001$ for both HAM-D and HAM-A, $p<0.05$) (Figures 3). We also noticed that the SN volume-to-midbrain volume ratio (SNVR) statistically increased to

22.4% on the right side ($p=0.002$, $p<0.05$) (Figure 4) and to 12.7% on the left side ($p=0.01$, $p<0.05$) (Figure 4) in MDD patients respect to the control group. Correlation analysis revealed a statistically significant negative correlation between age and the volumes of both the left and right SN respectively in the MDD group ($p=0.015$, $p=0.05$; $p<0.05$) (Table 3).

Table 1. Demographic data and clinical characteristics of MDD patients and healthy controls

	Controls (Mean±SD)	MDD (Mean±SD)
Age (year)	46.27±14.94	44.30±13.98
Female/male	(18/15)	(28/5)
HAM-D score	2.30±1.31	17.48±6.03*
HAM-A score	3.00±1.15	17.58±6.31*

MDD: major depressive disorder, HAM-D: Hamilton rating scale for depression, HAM-A: Hamilton rating scale for anxiety, SD: standard deviation. * Both HAM-D and HAM-A scores were higher in MDD group significantly in comparison to HC ($p=0.001$, $p<0.05$)

Table 2. Mean volumes of brain regions in MDD and control groups

Brain regions	Control (cm ³) Mean±SD	MDD (cm ³) Mean±SD	P value
LEFT SN	0.149±0.043	0.164±0.036	0.144
RIGHT SN	0.122±0.035	0.146±0.045	0.023
LEFT MB	2.648±0.382	2.611±0.446	0.791
RIGHT MB	3.169±0.493	3.102±0.522	0.598
TOTAL MB	5.817±0.860	5.713±0.950	0.679
LEFT SNVR	0.056±0.011	0.063±0.011	0.010
RIGHT SNVR	0.038±0.008	0.047±0.013	0.002

MDD: major depressive disorder, SD: standard deviation, SN: substantia nigra, MB: midbrain, SNVR: substantia nigra volume ratio

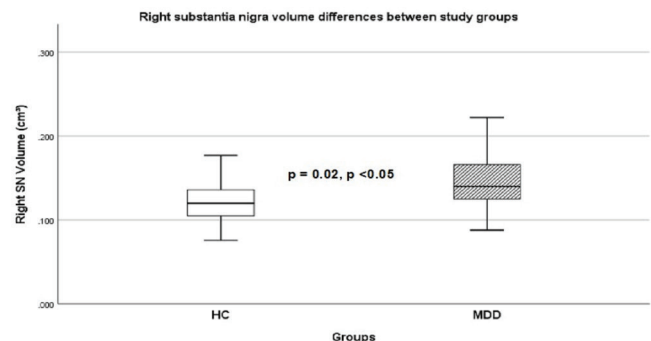


Figure 2. Box plot showing right side substantia nigra volume differences between MDD group and healthy controls. MDD: Major depressive disorder, SN: Substantia nigra, HC: Healthy controls

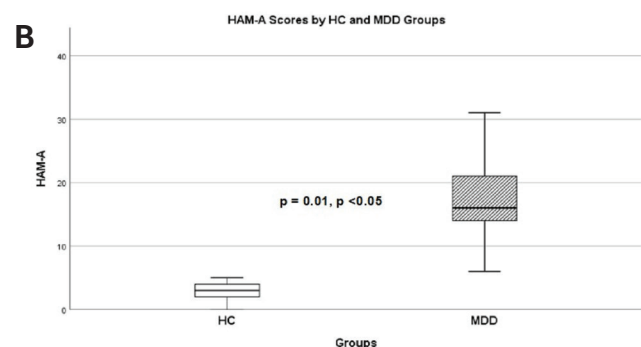
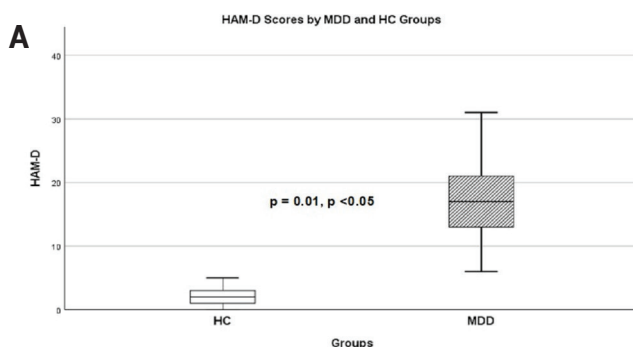


Figure 3. A. Box plot of HAM-D score differences between MDD group and healthy controls, B. Box plot of HAM-A score differences between MDD group and healthy controls. MDD: major depressive disorder, HC: healthy controls, HAM-D: Hamilton Rating Scale for depression, HAM-A: Hamilton Rating Scale for anxiety

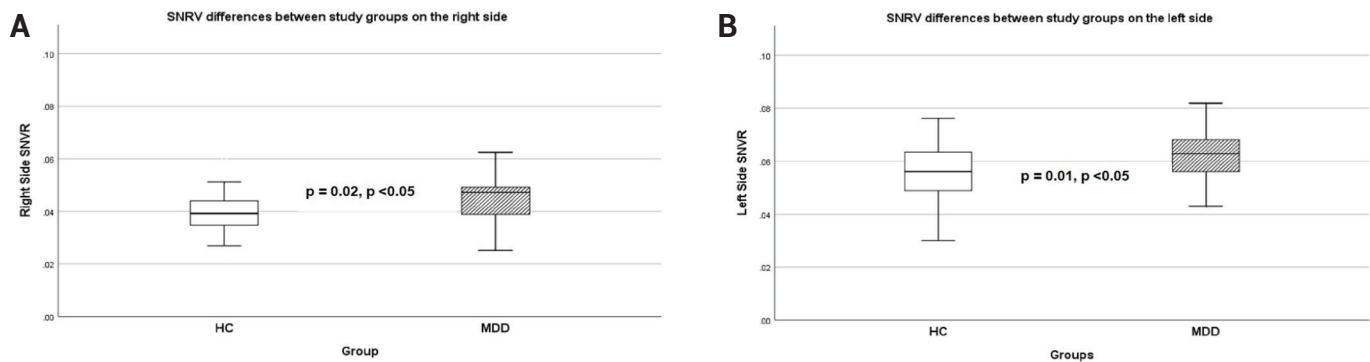


Figure 4. A. Box plot of right SN to midbrain volume ratio (SNVR) differences between MDD group and healthy controls, B. Box plot of left SN to midbrain volume ratio (SNVR) differences between MDD group and healthy controls, HC: healthy controls, MDD: major depressive disorder, SN: substantia nigra, SNV: substantia nigra volume ratio

Table 3. Correlation between average volumes of brain regions in the MDD group and age, HAM-D, and HAM-A scores

		Left SN	Right SN	Left MB	Right MB	Total MB	Left SNVR	Right SNVR
Age	r	-0.422	-0.343	-0.260	-0.271	-0.271	-0.285	-0.208
	p	0.015	0.050	0.144	0.128	0.127	0.108	0.246
HAM-D	r	0.187	-0.124	0.296	0.210	0.255	-0.064	-0.264
	p	0.296	0.491	0.094	0.240	0.152	0.722	0.138
HAM-A	r	0.020	-0.193	0.152	0.050	0.099	-0.101	-0.245
	p	0.914	0.281	0.400	0.781	0.585	0.577	0.169

MDD: major depressive disorder, HAM-D: Hamilton rating scale for depression, HAM-A: Hamilton rating scale for anxiety, SN: substantia nigra, MB: midbrain, SNVR: substantia nigra volume ratio

DISCUSSION

MDD is a clinically heterogeneous, multifactorial condition. In our study, we found an increase in the volume of the right SN and the bilateral SN volume to midbrain ratio in patients with MDD. The identification of these alterations shows potential for refining diagnosis and advancing targeted therapeutic interventions in the context of MDD (19,20). The SN is a crucial component of the reward pathway, termed as the limbic-cortical-striatal-pallidal-thalamic circuit. Numerous studies have indicated volumetric differences in brain regions associated with this pathway in MDD, suggesting that functional and volumetric alterations in these regions could play a significant role in MDD pathogenesis (21-24). Furthermore, several neuroimaging studies have shown volume reductions in prefrontal cortex areas, anterior cingulate cortex, hippocampus, amygdala, and subcortical brain regions such as the basal ganglia in MDD patients (25,26).

A thorough review of the literature revealed prior studies directly investigating SN volume in Parkinson's disease but found a scarcity of such studies for MDD (27-32). However, volumetric or pathophysiological changes and dopaminergic dysregulation in the SN have been reported in several neuropsychiatric disorders. Gao et al. observed reductions in bilateral SN volume and decreased functional connectivity in the left SN in patients with traumatic brain injury, emphasizing the association of these structural and functional changes with increased anxiety and depressive symptoms (14). Kempton et al. found an increase in SN volume in patients with bipolar disorder (33). Moreover, in a study conducted on schizophrenia patients, an increase

in the size of SN dopaminergic neurons' nucleoli and nuclei was demonstrated (27). In addition, the prevalence of depression accompanying schizophrenia was found to be 28.6% in a meta-analysis (34). The changes in SN volume observed in various neuropsychiatric disorders are not only consistent with our findings but also support the hypothesis that volumetric and functional alterations in the SN and its connected brain regions are associated with depressive symptoms.

In addition to studies measuring the volumes of brain regions, positron emission tomography (PET) imaging studies have reported a significant decrease in dopamine transporter activity in patients with MDD compared to healthy subjects, suggesting a reduction in dopaminergic neurotransmission, a key neurochemical mechanism implicated in the pathophysiology of depression (35,36). Based on ex vivo immunohistochemical measurements in the human brain, approximately 68% of all dopaminergic neurons identified in the midbrain are in the SNc, and 12% are in the ventral tegmental area (37). Dubol et al. found that individuals with depression have lower levels of dopamine transporters in upper midbrain areas, including the SN, ventral tegmental area, and the right putamen region. They suggested that the decrease in dopamine transporter levels could result from impaired dopaminergic function, structural changes in dopaminergic neurons, or both (35). Another study associated hyperintensity in the SN observed in patients with MDD with functional impairment in the nigrostriatal dopaminergic system (29). Therefore, alterations in dopaminergic neuron morphology and function in MDD may underlie the volumetric and intensity changes observed in the SN, suggesting a role for SN

structural plasticity in the pathophysiology of depression.

Several meta-analyses have emphasized that variations in brain region volumes among individuals with MDD may be influenced by disease progression, the age at which the disease manifests, and the administration of antidepressant medication (21,38). In MRI investigations addressing the timing of disease initiation in MDD, reductions in gray matter volume were noted in early-onset cases within the right fusiform gyrus, right middle temporal gyrus, and right posterior cingulate cortex. Conversely, augmented gray matter volume was discerned in the right middle occipital gyrus and left middle temporal gyrus in instances of late-onset (39). Another examination involving MDD patients with a later onset revealed heightened thickness in the right prefrontal cortex and orbitofrontal cortex compared to those with an early onset. Moreover, onset before the age of 30 is considered early onset in the literature (40). Considering that our study's average participant age exceeded 30, and an elevation in SN volume was noted in the patient cohort, our findings align with these established patterns. Observed alterations in volume associated with the age at which the disease begins could stem from distinct pathological mechanisms or represent compensatory responses.

A limited sample size and the unavailability of measures for dopaminergic neurotransmission activity constrain the limitations of our study.

CONCLUSION

In conclusion, the investigation of structural and functional alterations within the SN in MDD via neuroimaging methods holds potential utility for clinicians in MDD diagnosis and disease progression assessment. Longitudinal neuroimaging inquiries can shed light on the temporal dynamics of SN volume changes, elucidating whether these changes are constant or progressive. Additionally, such studies can elucidate how SN volume alterations correlate with variables such as antidepressant medication use, disease severity or patient age. The detailed analysis of the SN's structural changes in MDD is poised to play a significant role in understanding the fundamental pathogenesis of the disease.

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Conflict of interest: The authors have no conflicts of interest to declare.

Ethical approval: Ethical approval was taken from Çanakkale 18 Mart University, Non-interventional Clinical Researchers Ethical Committee (2013/75).

REFERENCES

1. Pitsillou E, Bresnehan SM, Kagarakis EA, et al. The cellular and molecular basis of major depressive disorder: towards a unified model for understanding clinical depression. *Mol Biol Rep.* 2020;47:753-70.

2. WHO. Depression and other common mental disorders: global health estimates. Vol. 24. Geneva: World Health Organization, 2017;8-16.
3. Gutiérrez-Rojas L, Porras-Segovia A, Dunne H, et al. Prevalence and correlates of major depressive disorder: a systematic review. *Braz J Psychiatry.* 2020;42:657-72.
4. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA.* 2003;289:3095-105.
5. Beyer JL, Krishnan KRR. Volumetric brain imaging findings in mood disorders. *Bipolar Disord.* 2002;4:89-104.
6. Delgado PL. Depression: the case for a monoamine deficiency. *J Clin Psychiatry.* 2000;61:7-11.
7. Perez-Caballero L, Torres-Sanchez S, Romero-López-Alberca C, et al. Monoaminergic system and depression. *Cell Tissue Res.* 2019;377:107-13.
8. Stahl SM. Stahl's essential psychopharmacology: neuroscientific basis and practical applications. In: *The Monoamine Hypothesis of Depression.* 5th edition. Cambridge University Press, 2021;264.
9. Neuroanatomy, substantia nigra. <https://www.ncbi.nlm.nih.gov/books/NBK536995> access date 16.08.2023
10. Güzelad Ö, Özkan A, Parlak H, et al. Protective mechanism of Syringic acid in an experimental model of Parkinson's disease. *Metab Brain Dis.* 2021;36:1003-14.
11. Dallé E, Mabandla MV. Early life stress, depression and parkinson's disease: a new approach. *Mol Brain.* 2018;11:1-13.
12. Chinta SJ, Andersen JK. Dopaminergic neurons. *Int J Biochem Cell Biol.* 2005;37:942-6.
13. Blomstedt P, Hariz MI, Lees A, et al. Acute severe depression induced by intraoperative stimulation of the substantia nigra: a case report. *Parkinsonism Relat Disord.* 2008;14:253-6.
14. Gao L, Xue Q, Gong S, et al. Structural and functional alterations of substantia nigra and associations with anxiety and depressive symptoms following traumatic brain injury. *Front Neurol.* 2022;13:719778.
15. Hwang KS, Langley J, Tripathi R, et al. In vivo detection of substantia nigra and locus coeruleus volume loss in Parkinson's disease using neuromelanin-sensitive MRI: Replication in two cohorts. *PLoS One.* 2023;18:e0282684.
16. Jiang H, Van Zijl PC, Kim J, et al. DtiStudio: resource program for diffusion tensor computation and fiber bundle tracking. *Comput Methods Programs Biomed.* 2006;81:106-16.
17. Roberts N, Puddephat M, McNulty V. The benefit of stereology for quantitative radiology. *Br J Radiol.* 2000;73:679-97.
18. Faria AV, Hoon A, Stashinko E, et al. Quantitative analysis of brain pathology based on MRI and brain atlases—applications for cerebral palsy. *Neuroimage.* 2011;54:1854-61.
19. Johansen-Berg H, Gutman DA, Behrens TE, et al. Anatomical connectivity of the subgenual cingulate region targeted with deep brain stimulation for treatment-resistant depression. *Cereb Cortex.* 2008;18:1374-83.

20. Cacciola A, Milardi D, Anastasi GP, et al. A direct cortico-nigral pathway as revealed by constrained spherical deconvolution tractography in humans. *Front Hum Neurosci*. 2016;10:374.
21. Schmaal L, Veltman DJ, Van Erp TG, et al. Subcortical brain alterations in major depressive disorder: findings from the ENIGMA major depressive disorder working group. *Mol Psychiatry*. 2016;21:806-12.
22. Goldstein Ferber S, Weller A, Yadid G, Friedman A. Discovering the lost reward: critical locations for endocannabinoid modulation of the cortico-striatal loop that are implicated in major depression. *Int J Mol Sci*. 2021;22:1867.
23. Jiang Y, Zou M, Wang Y, Wang Y. Nucleus accumbens in the pathogenesis of major depressive disorder: a brief review. *Brain Res Bull*. 2023;196:68-75.
24. Rigucci S, Serafini G, Pompili M, et al. Anatomical and functional correlates in major depressive disorder: the contribution of neuroimaging studies. *World J Biol Psychiatry*. 2010;11:165-80.
25. Öngür D, Price JL. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cereb Cortex*. 2000;10:206-19.
26. Wise T, Radua J, Via E, et al. Common and distinct patterns of grey-matter volume alteration in major depression and bipolar disorder: evidence from voxel-based meta-analysis. *Mol Psychiatry*. 2017;22:1455-63.
27. Williams MR, Galvin K, O'sullivan B, et al. Neuropathological changes in the substantia nigra in schizophrenia but not depression. *Eur Arch Psychiatry Clin Neurosci*. 2014;264:285-96.
28. Ziegler DA, Wonderlick JS, Ashourian P, et al. Substantia nigra volume loss before basal forebrain degeneration in early Parkinson disease. *JAMA Neurol*. 2013;70:241-7.
29. Hoepfner J, Prudente-Morrissey L, Herpertz SC, et al. Substantia nigra hyperechogenicity in depressive subjects relates to motor asymmetry and impaired word fluency. *Eur Arch Psychiatry Clin Neurosci*. 2009;259:92-7.
30. Ogisu K, Kudo K, Sasaki M, et al. 3D neuromelanin-sensitive magnetic resonance imaging with semi-automated volume measurement of the substantia nigra pars compacta for diagnosis of Parkinson's disease. *Neuroradiology*. 2013;55:719-24.
31. Huddleston DE, Langley J, Dusek P, et al. Imaging parkinsonian pathology in substantia nigra with MRI. *Curr Radiol Rep*. 2018;6:15.
32. Schwarz ST, Rittman T, Gontu V, et al. T1-weighted MRI shows stage-dependent substantia nigra signal loss in Parkinson's disease. *Mov Disord*. 2011;26:1633-8.
33. Kempton MJ, Haldane M, Jogia J, et al. Dissociable brain structural changes associated with predisposition, resilience, and disease expression in bipolar disorder. *J Neurosci*. 2009;29:10863-8.
34. Li W, Yang Y, An FR, et al. Prevalence of comorbid depression in schizophrenia: a meta-analysis of observational studies. *J Affect Disord*. 2020;273:524-31.
35. Dubol M, Trichard C, Leroy C, et al. Lower midbrain dopamine transporter availability in depressed patients: report from high-resolution PET imaging. *J Affect Disord*. 2020;262:273-7.
36. Meyer JH, Krüger S, Wilson AA, et al. Lower dopamine transporter binding potential in striatum during depression. *Neuroreport*. 2001;12:4121-5.
37. Schulz J, Zimmermann J, Sorg C, et al. Magnetic resonance imaging of the dopamine system in schizophrenia—a scoping review. *Front Psychiatry*. 2022;13:925476.
38. Yüksel D, Engelen J, Schuster V, et al. Longitudinal brain volume changes in major depressive disorder. *J Neural Transm (Vienna)*. 2018;125:1433-47.
39. Shen Z, Cheng Y, Yang S, et al. Changes of grey matter volume in first-episode drug-naive adult major depressive disorder patients with different age-onset. *Neuroimage Clin*. 2016;12:492-8.
40. Shen Z, Jiang H, Cheng Y, et al. Association of cortical thickness with age of onset in first-episode, drug-naive major depression. *Neuroreport*. 2019;30:1074-80.



The Role of Folic Acid on PC3 Prostate Cancer Cell Line

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Abstract

Aim: Prostate cancer (PCa), one of the most common malignant solid tumors, has become a significant and rapidly increasing global health concern for men. One of the vitamins in the B group that is essential in decreasing the risk of cancer is folic acid (FA). However, the protective effects of FA against PCa are insufficiently examined, and the underlying mechanism is still unknown. In this study, androgen-nonresponsive (PC3) human PCa was used to get a better understanding of the effect of FA on cell proliferation.

Material and Method: In the present study, the MTT assay was used to assess FA's inhibitory effect on cellular proliferation. Additionally, all groups underwent the TUNEL immunofluorescence staining procedure to identify apoptosis in the PC3 cell line.

Results: The most appropriate cytotoxic dose was determined to be the 24-hour FA values. When apoptotic TUNEL staining was evaluated in the PC3 cell line, FA significantly increased apoptosis. There was not a significant difference observed between the docetaxel (Dtx) and FA groups in terms of TUNEL-positive cell immunoreactivity in the PC3 cell line. There was no apparent distinction in the immunoreactivity intensity of TUNEL-positive cells in these groups.

Conclusion: The present study provides a fresh perspective on the fundamental mechanism underlying FA's capability to prevent PC3 cancer cells from proliferating. Our findings suggest that FA effectively inhibits PC3 cell line proliferation through the upregulation of apoptosis. Consequently, FA may be a potential novel cytotoxic and therapeutic strategy in the treatment of PCa disease.

Keywords: Folic acid, prostate cancer, docetaxel, apoptosis

INTRODUCTION

Cancer (an abnormal and uncontrolled proliferation of cells) is one of the world's leading causes of death. The World Health Organization (WHO) predicts that 11 million people receive a cancer diagnosis each year and that 7 million people die due to cancer-related causes (1). As a result, cancer is currently one of the deadliest diseases, and over the past few decades, advances in medical technology have produced a variety of options for treating cancer (2). Traditional chemotherapy has several limitations, including high toxicity, ineffective tumor-specific delivery, and the potential to cause multi-drug resistance (3). Prostate cancer (PCa) continues to be the cancer that is most prevalent in men worldwide and the third-largest cause of cancer-related mortality (4). A PCa

survey conducted in 2019 founded that there were about 1,64,690 new cases and 29,430 deaths in the US. However, hormonal therapy, chemotherapy, radiation therapy, and radical prostatectomy (surgery) were the usual methods utilized to treat PCa. Cancer patients experience a variety of side effects from their treatment, including decreased sexual desire, incontinence, infertility, and hormone-based side effects (5). The high mortality rate among PCa patients is the primary cause of the early detection of PCa. Therefore, to increase patient survival rates, it is essential to develop rapid and early diagnostic strategies for PCa.

One crucial water-soluble B vitamin is folate, which can be found in a variety of foods, including legumes, fruit juices, and green leafy vegetables. Naturally occurring and non-immunogenic, folic acid (FA) has a small molecular

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weight. It is transformed into folate within the body, which has a strong affinity for the receptor (6). FA is the synthetic form of this vitamin that is typically found in foods that have been fortified, particularly grains and cereals, as well as supplements. While FA is the oxidized form of folate that contains a single glutamate moiety and is easily bioavailable, folate in the diet is present in a reduced form with side chains that contain multiple glutamate residues and must be absorbed through either oxidation or hydrolysis. Dietary folate has a bioavailability that varies from 10 to 98% (7). Due to its involvement in both nucleotide synthesis and methylation, folate has been the subject of much research (8). FA is a cheaply non-immunogenic chemical that functions as a great targeted ligand in a variety of cancer cells, including those from the brain, ovary, prostate, breast, lung, and colorectal cancer (9). Studies have indicated that FA-targeting nanodrugs have promising potential applications in a range of cancer types. FA is a high-affinity medication that targets the folate receptor (10). It has been found that some cancers, such as neoplasms of the colon, cervix, lung, esophageal, and pancreatic, were positively correlated with lower dietary FA consumption and low circulatory folate status (11).

Within the taxoid family, docetaxel (Dtx) is a semisynthetic anticancer mitotic ("antineoplastic" or "cytotoxic") chemotherapy drug. According to Rivero-Buceta (2019) (12), patients with hormone-refractory metastatic PCa are advised to consider Dtx as an optional treatment option. It has been established by many studies that Dtx binds to β -tubulin, interfering with the microtubules' normal polymerization dynamics, dividing cells during mitosis, connecting to microtubules, and inducing apoptosis (13). Drug resistance, however, is defined as a decrease in the effects of chemotherapy drugs such as Dtx. In this context, one of the main obstacles to successful chemotherapy is considered to be drug resistance.

Here are some indications of the cytotoxicity and apoptotic effects of FA. Overall, we hypothesized that treating the PC3-PCa cell line with FA reduces cell proliferation by inhibiting apoptosis. The aim of the current study is to determine whether FA increases the cytotoxicity of the PC3-PCa cell line in order to test the hypothesis. Future patient survival rates would be significantly impacted by the development of efficient Dtx chemotherapy, which would have a considerable impact on patient survival rates in the future.

MATERIAL AND METHOD

The study does not require ethics committee approval.

Cell Line

The androgen-independent human prostate cell line PC3 (ATCC. CRL1435TM) was utilized. RPMI-1640 (Thermo Fisher Scientific, USA) medium was used to grow the cells. To make complete media, 10% fetal bovine serum (Thermo Scientific, USA), 1% L-glutamine (Thermo Scientific, USA),

and 1% penicillin and streptomycin (Thermo Scientific, USA) were added to RPMI.

Cell Viability Assay

FA (Merck, Germany) was diluted in dimethyl sulfoxide (DMSO, Sigma, MO, USA) (14). 1 mM stock solution was made. The Dtx (160 mg/8 mL, Koçak Farma, Istanbul) was supplied in liquid form. The MTT assay was used to evaluate the cell proliferation as previously described (15). Following cell culture, PC3 cells were treated with FA at doses of 1, 10, 100 μ M and 1 mM or Dtx at doses of 1, 4, 16, and 64 nM. For every concentration, four duplicate samples were analyzed. The IC₅₀ values of FA and Dtx were calculated statistically.

Cell Apoptosis Assay

Cells were seeded in 12-well plates at a density of 5×10^5 cells per well. Then, cells were incubated with the IC₅₀ dose of FA or Dtx. The ApopTag Fluorescein In Situ Apoptosis Detection Kit (EMD Millipore, Darmstadt, Germany) was used as previously described (16). To observe cells, an Olympus BX51 fluorescent microscope (Tokyo, Japan) was used to evaluate preparations. Ten different fields of view in total were chosen at random for quantitative analysis, and the immunoreactivity of TUNEL-positive cells was measured with Image J software (Bethesda, USA).

Statistical Analysis

The Graph-Pad Prism 9.4.1 program (San Diego, CA, USA) was used for the statistical analysis. The data's conformance to the normal distribution was assessed using the Kolmogorov-Smirnov test. To examine comparisons between two groups, a one-way ANOVA was used, while for comparisons among multiple groups, Bonferroni's multiple comparisons test was used. The data is shown as the mean \pm standard deviation.

RESULTS

Effects of FA and Dtx on the growth of PC3 human PCa cells: Following treatment for 24, 48, and 72 h, the FA's and Dtx's inhibitory effects on the PC3 PCa cell lines were evaluated by an MTT assay. Cell viability in the PC3 cell lines decreased with dose and the passage of time upon treatment with FA or Dtx. The IC₅₀ values of the effect of FA or Dtx on PC3 cells were 116.8 μ M and 3.69 nM at 24 h, respectively (Figures 1 and 2). These FA and Dtx concentrations were used for further investigations based on this dose-effect relationship.

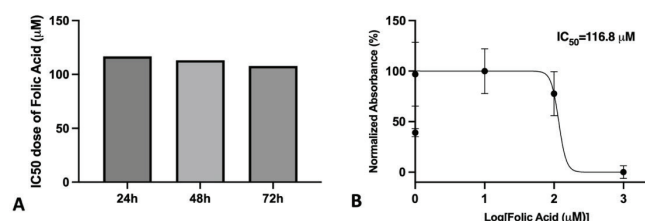


Figure 1. 1A. Change in FA IC₅₀ dose depending on time. 1B. Dose response curves for FA (24h)

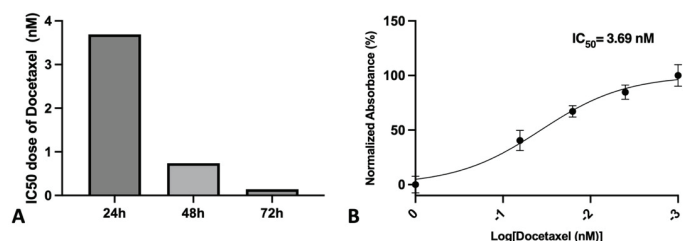


Figure 2. 2A. Change in Dtx IC50 dose depending on time. 2B. Dose response curves for Dtx (24h)

Effects of FA and Dtx on the apoptosis of PC3 human PCa cells: To examine the mechanism underlying the cell death effects of FA and Dtx, the TUNEL assay was performed. As shown in Figure 3, apoptosis was triggered by FA and Dtx in PC3 cells. After FA and Dtx treatment, nuclear fragmentation was detected in PC3 cells. Compared with the control, treatment with FA significantly increased the proportion of TUNEL-positive apoptotic cells ($p=0.0005$). There was a noticeable increase in TUNEL-positive apoptotic cells in PC3 cells when comparing the Dtx group to the control group ($p<0.001$). There was an increase in TUNEL positive apoptotic cells in the Dtx group compared

to the FA group. But this was not statistically significant ($p<0.001$) (Table 1).

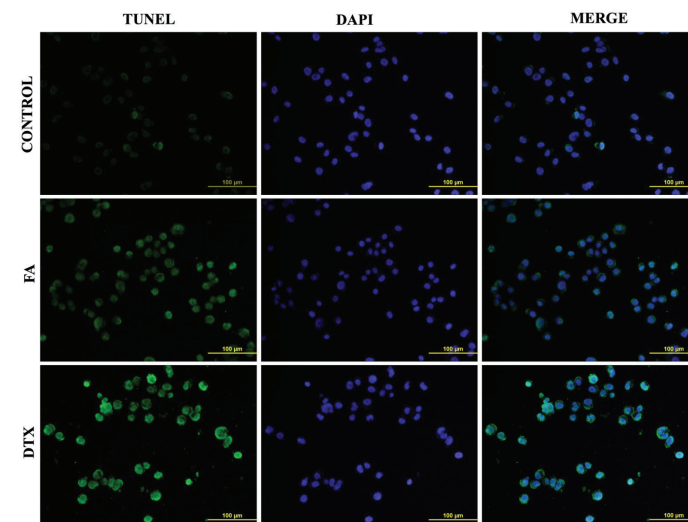


Figure 3. TUNEL images of the PC-3 cell line treated with FA and Dtx. The apoptotic bodies released in the cells were detectable under the fluorescent microscope as green reflections

Table 1. TUNEL statistical analysis results of PC-3 human PCa cell lines treated with FA or Dtx

	Control	FA	Dtx	p
Immunoreactivity intensities of TUNEL	(1.78± 0.38) ^a	(3.35± 0.77) ^b	(3.95± 0.49) ^b	<0.0001

Data are expressed as mean ± st. deviation. p: refers to the significance of the difference between the groups. The same lowercase letters in the same row show similarity between groups, and different lowercase letters indicate differences between groups. P value of <0.05 was used for significance

DISCUSSION

It is especially crucial to consume exogenous folates, such as FA, in order to replenish the intracellular folate pool in rapidly dividing cells, such as cancer cells (17). Thus, it's critical to ascertain whether FA causes or prevents cell damage. This study examined how FA administration's targeted mechanism affected the PC3 PCa cell line's capacity to undergo apoptosis. Few epidemiological studies examined the impact of dietary folic acid or folate on the incidence of prostate cancer. Moreover, taking the inconsistency of study designs into consideration, it comes as no surprise that their conclusions vary so dramatically. Therefore, with growing experimental evidence indicating that folic acid contributes to prostate progression, continued research is required to further delineate these complex relationships (18). We therefore turned to experimental models to glean any clues about the role of folate in prostate carcinogenesis.

One of the numerous cancers associated with chromosome rearrangement, DNA uracil mismatch, and epigenetic modification is PCa (19). Even though chemotherapy is frequently used to treat cancer, most chemotherapy drugs have harmful side effects and organ toxicity. The medications' nonselective distribution as well as poor pharmaco-bioavailability are the main causes of these issues. In order to overcome these limitations, it is essential to develop novel therapeutic systems that specifically target abnormal tissues while avoiding normal

ones. Fruits, dairy products, and green leafy vegetables are common sources of FA, an essential B vitamin that plays a major role in immune response (20). Currently, the exact mechanism by which FA inhibits the proliferation of tumors is still unknown.

FA is a ligand that specifically targets cancer cells and has a strong affinity for the overexpressed folate receptors found in the epithelium of cancer cells. On the other hand, overexpression of different molecular receptors is typically associated with cancer cells (21). There is an overexpression of folate receptors in certain tumors, such as cancers of the colon, breast, ovary, lung, and prostate. Because non-cancerous cells lack folate receptors, FA is an incredibly attractive ligand (22). After attaching to the folate receptor, FA and folate conjugates form endosomes that allow them to enter cells (23). Recent research has confirmed that both folate receptors (FR α and FR β) are expressed in pancreatic cancer (24). Additionally, reports have stated that PCa cells overexpress folate receptors (25).

It has been suggested that FA acts through the transfer of one-carbon units for methylation reactions and nucleotide biosynthesis through folate one-carbon metabolism. Consistent with structural and clinical observations, FA requires long-term supplementation to have a significant effect because nucleotide biosynthesis, DNA methylation, gene transcription, and expression all require sufficient reaction timescales in organisms (26).

Drug treatments for diseases will become possible once the mechanisms of apoptosis' cellular death are understood (27). A few research investigations have been carried out on the use of folate overexpression in treating PCa, despite the fact that it has been used to treat other forms of cancer (28). It was found that FA supplementation induced apoptosis in sentinel breast cancer cells by upregulating the expression of proapoptotic proteins (BAX, PARP). Nevertheless, FA supplementation was found to have no discernible impact on the expressions of PCNA, BCL-2, BCL-XL, and caspase-3 in the same study (29). When applied to MCF 7 and MDA-MB 23 lines, β -lactoglobulin nanoparticles and FA loaded with doxorubicin significantly inhibited cell proliferation and induced apoptosis (30). Additionally, it examined how FA affected the up- and down-regulation of Bak1 and Bclx expression in MCF-7 cells. The results showed that a cisplatin complex containing FA can considerably increase Bak1/Bclx ratios in contrast to cisplatin alone (31). Based on all of these findings, FA could be crucial in promoting apoptosis. Studies on the Bcl-2 protein family can provide a comprehensive understanding of the mitochondria-mediated apoptotic pathway, as they are the key regulators of apoptosis (32). Previous studies have shown that high-dose FA has an important effect on preventing gastric cancer (33). There have been no reports of FA's inhibitory effects on the PC3 PCa cell line as of yet. This is the first study that demonstrates that FA can effectively reduce proliferation, possibly by preventing the apoptotic pathway from being activated. When we evaluated our research in terms of apoptosis, we found that in PC3 cell lines, the FA group increased TUNEL-positive apoptotic cell numbers significantly more than the control group. Thus, it can be said that one useful step in the treatment of PCa may be the inclusion of targeting factors, including FA, in the complex structure.

CONCLUSION

Taken together, the study's findings showed that FA causes cytotoxicity in the PC3 cell line based on the MTT assay results. In PC3 PCa models, the FA group successfully increased the number of TUNEL-positive cells. Furthermore, the TUNEL assay clearly indicates that FA could potentially use in vitro apoptosis. In conclusion, despite being a necessary treatment option for PCa, chemotherapy presents challenges with regard to cost, efficacy, toxicity, and resistance. Additionally, the FA may be suggested as a promising addition to Dtx therapy, prolonging survival times in PCa models. Consequently, the findings indicate that the previously mentioned FA could prove beneficial for PCa treatment and monitoring with fewer adverse effects. Examining the mechanism underlying its impact on various tumor cells is suggested. The safety and efficacy of FA in PCa need to be determined through pre-clinical research in the field.

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Conflict of interest: The authors have no conflicts of interest to declare.

Ethical approval: The study does not require ethics committee approval.

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REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136:E359-86.
2. Wang Y, Shim MS, Levinson NS, et al. Stimuli-responsive materials for controlled release of theranostic agents. *Adv Funct Mater*. 2014;24:4206-20.
3. Lehto U-S, Tenhola H, Taari K, Aromaa A. Patients' perceptions of the negative effects following different prostate cancer treatments and the impact on psychological well-being: a nationwide survey. *Br J Cancer*. 2017;116:864-73.
4. Rawla P. Epidemiology of prostate cancer. *World J Oncol*. 2019;10:63-89.
5. Luo D, Wang X, Zeng S, et al. Prostate-specific membrane antigen targeted gold nanoparticles for prostate cancer radiotherapy: Does size matter for targeted particles. *Chem Sci*. 2019;10:8119-28.
6. Anirudhan T, Varghese S, Manjusha V. Hyaluronic acid coated pluronic F127/pluronic P123 mixed micelle for targeted delivery of paclitaxel and curcumin. *Int J Biol Macromol*. 2021;192:950-7.
7. Pieroth R, Paver S, Day S, Lammersfeld C. Folate and its impact on cancer risk. *Curr Nutr Rep*. 2018;7:70-84.
8. Friso S, Choi S-W. Gene-nutrient interactions and DNA methylation. *J Nutr*. 2002;132:2382S-7.
9. Cheng W, Nie J, Xu Lv, et al. pH-sensitive delivery vehicle based on folic acid-conjugated polydopamine-modified mesoporous silica nanoparticles for targeted cancer therapy. *ACS Appl Mater Interfaces*. 2017;9:18462-73.
10. Yao V, Berkman CE, Choi JK, et al. Expression of prostate-specific membrane antigen (PSMA), increases cell folate uptake and proliferation and suggests a novel role for PSMA in the uptake of the non-polyglutamated folate, folic acid. *Prostate*. 2010;70:305-16.
11. Stolzenberg-Solomon RZ, Chang S-C, Leitzmann MF, et al. Folate intake, alcohol use, and postmenopausal breast cancer risk in the prostate, lung, colorectal, and ovarian cancer screening trial. *Am J Clin Nutr*. 2006;83:895-904.
12. Rivero-Buceta E, Vidaurre-Agut C, Vera-Donoso CD, et al. PSMA-Targeted mesoporous silica nanoparticles for selective intracellular delivery of docetaxel in prostate cancer cells. *ACS Omega*. 2019;4:1281-91.
13. Katsumata N. Docetaxel: an alternative taxane in ovarian cancer. *Br J Cancer*. 2003;89:9S-15.
14. Önder GÖ, Goktepe Ö, Baran M, et al. Therapeutic potential of hesperidin: Apoptosis induction in breast cancer cell lines. *Food Chem Toxicol*. 2023;176:113791.

15. Genc S, Pennisi M, Yeni Y, et al. Potential neurotoxic effects of glioblastoma-derived exosomes in primary cultures of cerebellar neurons via oxidant stress and glutathione depletion. *Antioxidants (Basel)*. 2022;11:1225.
16. Baran M, Onder GO, Goktepe O, Yay A. Role of apoptosis and autophagy in folic acid-induced cytotoxicity of human breast cancer cells in vitro. *Fundam Clin Pharmacol*. 2024;38:126-38.
17. Hwang SY, Kang YJ, Sung B, et al. Folic acid is necessary for proliferation and differentiation of C2C12 myoblasts. *J Cell Physiol*. 2018;233:736-47.
18. Rycyna KJ, Bacich DJ, O'Keefe DS. Opposing roles of folate in prostate cancer. *Urology*. 2013;82:1197-203.
19. Yegnasubramanian S, Haffner MC, Zhang Y, et al. DNA hypomethylation arises later in prostate cancer progression than CpG island hypermethylation and contributes to metastatic tumor heterogeneity. *Cancer Res*. 2008;68:8954-67.
20. Craenen K, Verslegers M, Baatout S, Abderrafi Benotmane M. An appraisal of folates as key factors in cognition and ageing-related diseases. *Crit Rev Food Sci Nutr*. 2020;60:722-39.
21. Hassn Mesrati M, Syafruddin SE, Mohtar MA, Syahir A. CD44: a multifunctional mediator of cancer progression. *Biomolecules*. 2021;11:1850.
22. Purohit B, Kumar A, Mahato K, et al. Cancer cytosensing approaches in miniaturized settings based on advanced nanomaterials and biosensors. In: *Nanotechnology in modern animal biotechnology*. Elsevier. 2019;133-47.
23. Song H, Su C, Cui W, et al. Folic acid-chitosan conjugated nanoparticles for improving tumor-targeted drug delivery. *BioMed Res Int*. 2013;2013:723158.
24. Scaranti M, Cojocar E, Banerjee S, Banerji U. Exploiting the folate receptor A in oncology. *Nat Rev Clin Oncol*. 2020;17:349-59.
25. Omote S, Takata K, Tanaka T, et al. Over expression of folate receptor alpha is an independent prognostic factor for outcomes of pancreatic cancer patients. *Med Mol Morphol*. 2018;51:237-43.
26. Richmond RC, Sharp GC, Herbert G, et al. The long-term impact of folic acid in pregnancy on offspring DNA methylation: follow-up of the aberdeen folic acid supplementation trial (AFAST). *Int J Epidemiol*. 2018;47:928-37.
27. Elmore S. Apoptosis: a review of programmed cell death. *Toxicol Pathol*. 2007;35:495-516.
28. Bonvin D, Bastiaansen JA, Stuber M, et al. Folic acid on iron oxide nanoparticles: platform with high potential for simultaneous targeting, MRI detection and hyperthermia treatment of lymph node metastases of prostate cancer. *Dalton Trans*. 2017;46:12692-704.
29. Manshadi SD, Ishiguro L, Sohn K-J, et al. Folic acid supplementation promotes mammary tumor progression in a rat model. *PLoS One* 2014;9:e84635.
30. Kayani Z, Bordbar AK, Firuzi O. Novel folic acid-conjugated doxo-rubicin loaded β -lactoglobulin nanoparticles induce apoptosis in breast cancer cells. *Biomed Pharmacother*. 2018;107:945-56.
31. He C, Heidari Majd M, Shiri F, Shahraki S. Palladium and platinum complexes of folic acid as new drug delivery systems for treatment of breast cancer cells. *J Mol Struct*. 2021;1229:129806.
32. Popgeorgiev N, Sa JD, Jabbour L, et al. Ancient and conserved functional interplay between Bcl-2 family proteins in the mitochondrial pathway of apoptosis. *Sci Adv*. 2020;6:eabc4149.
33. Xiao SD, Meng XJ, Shi Y, et al. Interventional study of high dose folic acid in gastric carcinogenesis in beagles. *Gut*. 2002;50:61-4.



The Effect of Telehealth-Based Rehabilitation on Patient Reported Outcomes and Objective Clinical Measurements in Patients With Degenerative Meniscal Tear

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Abstract

Aim: The study aimed to compare the effectiveness of telehealth-based home exercises and conventionally prescribed home exercises in patients with degenerative meniscal tears.

Material and Method: A two-armed, randomized controlled study was conducted with 49 participants with degenerative meniscal disease. Patients were randomized into Telerehabilitation (TR=25) and Conventional Home Exercise Rehabilitation (CR=24) groups. The TR group provided video exercises and self-management education via an online platform. The same protocol was given to the CR group in the clinical setting. Pain with Visual Analog Scale, muscle strength with Hand-Held Dynamometer, proprioception with Baseline bubble inclinometer, functional status with Western Ontario and McMaster Universities Osteoarthritis Index, exercise adherence with Exercise Adherence Rating Scale, quality of life with Short Form-12 were evaluated at baseline and after eight weeks of intervention. In addition, satisfaction and usability were assessed with the Telemedicine Satisfaction and Usefulness Questionnaire at week 8.

Results: The TR group improved activity pain, proprioception, some parameters of the muscle strength outcomes, and exercise adherence scores ($p < 0.05$). The TR group was not superior to the CR group regarding pain at rest, quality of life and functional status ($p > 0.05$). In addition, 52 percent of the TR group reported high levels of satisfaction and usability.

Conclusion: Despite increased participation and satisfaction, the telerehabilitation group noticed improvements in clinician-based measures (proprioception, strength) but not in rest pain, function, and quality of life. As a result, telerehabilitation-based home exercises prescribed to these patient groups are more effective.

Keywords: Menisci, mobile health, self-care, video exercise

INTRODUCTION

Degenerative meniscal lesions are a widespread disease burden, particularly in middle-aged and older individuals (1). Although this type of lesion is mainly seen in the posterior horn of the medial meniscus, additionally overloading the joint, malalignment, and excessive body weight accelerate degenerative meniscus formation (2). The literature provides updated approaches (exercise, surgery) and discusses how appropriate treatment should be in degenerative meniscal lesions (3). Conservative and surgical treatment components are recommended in the treatment of degenerative meniscal lesions. Especially in

the last decade, conservative approaches have replaced arthroscopic surgical approaches in treating degenerative meniscal lesions (4). Hence, a conservative treatment component, including evidence-based physiotherapy, is frequently administered in degenerative meniscal tears (if there is no sign of locking or entanglement) (5). Effective approaches that constitute the most essential part of evidence-based physiotherapy and play a key role in individuals with this disease burden are exercise programs that increase muscle strength and function (6). Different studies have emphasized the positive effects of exercises on pain, muscle strength, and quality of life in individuals with degenerative meniscal tears (7,8).

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In recent years, health services have been prescribed to individuals through telecommunication technologies and access to health centers. Via remote telerehabilitation, physiotherapy applications are increasingly prescribed for individuals with musculoskeletal problems. With telerehabilitation, it is possible to meet with patients remotely, and evaluation, consultation, physiotherapy, and follow-up are alternative and low-cost methods (9,10). Physiotherapists can use different communication techniques and sound evidence-based strategies such as video exercises, video conferencing, self-management principles, e-mail, telephone, and messages (11). Telerehabilitation has been reported to positively affect pain and function when given simultaneously (real-time) with videoconferencing in individuals with musculoskeletal problems (12). Moreover, it has been reported that the evaluation of musculoskeletal disorders involving the knee through telerehabilitation is feasible and has good inter or intra-rater reliability (13).

Telerehabilitation services are gradually developing with the spread of telemedicine applications in musculoskeletal disorders (9). In another experiment, two methods (videoconference, telemedicine follow-up, and office-based follow-up) were compared in the postoperative follow-up of individuals who had arthroscopic meniscectomy and repair. In conclusion, it has been emphasized that telemedicine and traditional office-based follow-up are equivalent to each other in the postoperative follow-up of individuals who have undergone arthroscopic meniscectomy and repair, and the importance of telemedicine follow-up as an alternative method (14). As yet, there is no study evaluating the effects of telerehabilitation on clinical status, patient satisfaction, and quality of life using subjective and objective measurements in individuals with degenerative meniscal lesions followed by conservative treatment. In addition, degenerative meniscal injury usually involves middle-aged individuals, and middle-aged individuals may adapt more easily to tele-rehabilitation methods. Therefore, we aimed to conduct the present study in this population. The study aimed to compare the effectiveness of telehealth-based and conventional paper-based home exercises on patient-reported outcomes and objective clinical measures in patients with degenerative meniscal tears. We hypothesized that telerehabilitation-based home exercises would be more effective than traditional paper-based home exercises in patients with degenerative meniscus.

MATERIAL AND METHOD

Study Design and Participants

A randomized controlled trial was conducted in Muğla Sıtkı Koçman University, Department of Orthopedics and Traumatology. Forty-nine participants diagnosed with degenerative meniscus injury by an orthopedic specialist were included in the study. The trial is reported

according to the "CONsolidated Standards of Reporting Trials (CONSORT) stages and taken into account the recommendations of Standard Protocol Items: SPIRIT (Statement of Recommendations for Interventional Trials)" (15).

Inclusion criteria were; (1) individuals aged between 18 and 65, (2) individuals diagnosed with degenerative meniscus injury after clinical and radiological evaluations by an orthopedic specialist and decided to follow up with conservative treatment. Exclusion criteria from the study: (1) people with a history of surgery due to degenerative meniscus injury, (2) orthopedic and neurological conditions that could prevent evaluation and/or treatment, (3) conditions that may prevent communication in the evaluation and follow-up of individuals.

At the baseline, 85 individuals were recruited. However, 25 were excluded as they did not meet the inclusion criteria. A total of 60 patients were randomly allocated to the groups. Eleven individuals were excluded from the study for different reasons. As a result, 49 patients, including 24 conventional home exercise rehabilitation (CR) and 25 telerehabilitation (TR), were analyzed (Figure 1).

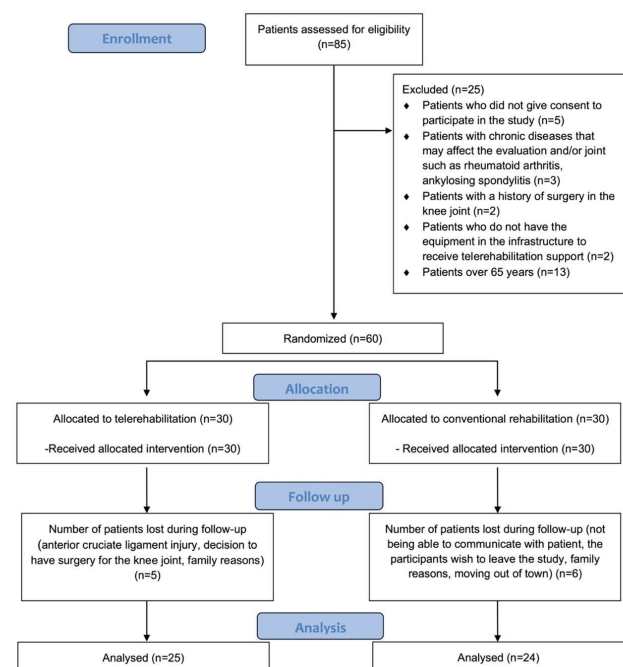


Figure 1. CONSORT flow chart of the study

Recruitment

Participants who met all criteria were informed about the study. The purpose, method, and possible risks of the study were explained to the individuals diagnosed with degenerative meniscal injury within the scope of the information. Written informed consent was obtained from individuals who agreed to participate in the study.

Sample Size

According to a power analysis that was calculated with G-Power 3 (16), regarding the reference values of the

study with identical methodology (17), the effect size was calculated as 1.00. At least 23 individuals were calculated to be required for each group, with a power of 0.95 and a confidence interval of 0.05.

Ethical Consideration

The study protocol was approved by the ethics committee of Muğla Sıtkı Koçman University (Decision dated 05/01/2022 and numbered 1/IV). The study protocol was registered (ClinicalTrials.gov Identifier: NCT05233839).

Randomization

The study's allocation method was determined by the order of patients' arrival using the random assignment table generated by the "National Institutes of Health National Cancer Institute Clinical Trial Randomization Tool."

Interventions

The TR group received video-based exercise and self-management education. The CR group received the identical paper-based exercise and education protocol. The exercise program included stretching and strengthening exercises for lower extremity muscles given to individuals diagnosed with degenerative meniscus injury as part of conservative treatment (Additional File 1) (Figure 2). All individuals were asked to do the exercises for eight weeks (10 repetitions once a day). In addition, the exercises were tailored to the individual's needs. Self-management criteria include educational information such as joint protection techniques and methods of coping with pain (Additional File 2). The individuals in the TR group were shown home exercises and self-management criteria in the clinic on the first day, and they were asked to do it correctly. Relevant documents were sent to individuals' mobile phones via the online platform. Similarly, the individuals in the CR group were shown the exercises and self-management criteria in the clinic on the first day. However, an exercise brochure with pictures and explanations was given instead of a video.

Exercise 1: Knee extension in sitting position



Exercise 2: Isometric knee extension with towel compression below the knee in the long sitting position

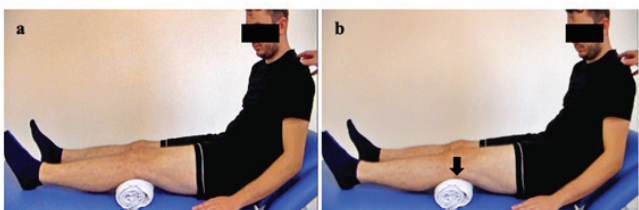


Figure 2. Exercise sample from the rehabilitation protocol

Pain intensity of individuals in both groups "Visual Analog Scale (VAS), functionality Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), proprioception Baseline bubble inclinometer, muscle strength Lafayette hand-held dynamometer, exercise compliance Exercise Adherence Rating Scale (EARS), quality of life Short Form-12 (SF-12) measured at the baseline and 8th week. At the end of the study, patient satisfaction was evaluated with the Telemedicine Satisfaction and Usefulness Questionnaire (TSUQ)".

Visual Analog Scale

The study evaluated pain severity with the VAS. Individuals participating in the study were asked to mark the severity of pain (0: no pain, 10: maximum pain) on a 10 cm straight line. Pain severity was evaluated for both rest and activity status (18).

Western Ontario and McMaster Universities Osteoarthritis Index

Individuals' level of functionality was assessed with the WOMAC. WOMAC is a patient reporting scale comprising 24 questions with three sub-dimensions: pain, stiffness, and physical function. Each question is evaluated on a Likert scale between 0 (none) and 4 (extreme). An increase in the score in WOMAC indicates more or worse symptoms, maximum restrictions, and poor health (19).

Proprioception Measurement

Proprioception was evaluated by a Baseline bubble inclinometer (model 12-1056, Fabrication Enterprises; White Plains, New York) with the active angle repetition test in a closed kinetic chain position, with the individual standing. The inclinometer was placed on the distal part of the tibial tuberosity. The individual was asked to perform a single leg squat from the full knee extension position while standing. He was asked to stay at 30° knee flexion and return to full knee extension, keeping his position for 5 seconds. This movement was repeated three times. Then, without giving the stop command, the individual was asked to reach the targeted 30° knee flexion as before. In the same way, this movement was repeated three times. To prevent possible loss of balance during the test, the individual was allowed to receive support with the help of one hand. The difference between the targeted angle and the angle made by the individual in each test repetition was determined as "absolute angular error". The arithmetic mean of the difference between the targeted angle and the angle made by the individual was calculated as "The Relative Angular Error (RAE)" and recorded (20,21).

Muscle Strength Test

The strength of the quadriceps femoris muscle was measured in "Kilogram (kg)" with a Hand-Held Dynamometer (model-01165, Lafayette Instrument®, Lafayette IN, USA). For the test, the individual was seated in a standard chair. Knee extension strength was measured with a dynamometer placed two fingers above

the ankle from the front of the leg. The individual was asked to bring the knee from 90° flexion to knee extension with maximum force. Measurements were made three times. The individual was allowed to rest for 120 seconds between measurements. The highest muscle strength measurement value was recorded (22).

Exercise Adherence Rating Scale

The individual's level of exercise compliance was evaluated with the EARS. EARS consists of six items that individuals can answer themselves. Each item is scored between 0 and 4. The scoring of the 1st, 4th, and 6th items is done in reverse. Individuals who score high on the scale also have high exercise compliance (23).

Short Form 12

The SF-12 evaluates individuals' quality of life. The scale has sub-dimensions similar to SF-36. Items related to physical and emotional roles are answered as yes/no. Other items are Likert type, with response options ranging from three to six. Physical dimension-12 and mental dimension-12 scores range from 0 to 100. Higher scores indicate better health (24).

Telemedicine Satisfaction and Usefulness Questionnaire

The TSUQ evaluated individuals' satisfaction levels and usability concerning telerehabilitation." Each item in the questionnaire is evaluated with a 5-point Likert scale. TSUQ's total score ranges from 21 to 105 (25).

Statistical Analysis

All analysis was conducted by SPSS (Statistical Package for Social Sciences) for Windows v25.0 (SPSS Inc, IBM Corp, Armonk, New York). In the statistical analysis test decision, the conformity of all the data to the normal distribution was examined by conducting the One-sample Kolmogorov-Smirnov test. Parametric and non-parametric tests were used according to the homogeneity of the data. Independent Sample t-test was used to compare independent group differences when parametric test assumptions were met; when parametric test assumptions were not met, the Mann-Whitney U test was used to compare independent group differences. In addition, chi-square analysis was used for categorical variables in independent group comparisons. In dependent group comparisons, when parametric test assumptions are provided, the Paired t-test is used; when parametric test assumptions are not met, the Wilcoxon signed-rank test is used. The statistical significance level was set at $p < 0.05$.

RESULTS

Patient Characteristics

The study was completed with 49 patients (41.08±9.8 years, 25 female, 24 male). Table 1 shows the demographic and clinical characteristics of the participants. There was no significant difference in participants' baseline data.

Pain

The change in pain scores is given in Table 2. In group comparisons, the r-VAS value improved significantly in the telerehabilitation group (TRG) ($p < 0.001$) and conventional home exercise rehabilitation group (CRG) ($p < 0.01$) after treatment compared to pretreatment. There was a significant improvement in a-VAS values in both groups ($p < 0.001$). The a-VAS values showed more significant differences in TRG in the adjusted analyses, comparing the difference in change between the initial and final assessments of the groups ($p = 0.03$). However, no significant difference was found in other parameter comparisons between groups ($p > 0.05$).

Function

The analyses of the WOMAC scores of the groups are summarized in Table 2. We found significant in-group improvement in all WOMAC subscores and total scores ($p < 0.01$). In between-group analysis, no significant difference was found in any of the parameters ($p > 0.05$).

Quality of Life

Data on health-related quality of life are presented in Table 2. We reported a significant improvement in SF-12 physical component summary (PCS) and SF-12 mental component summary (MCS) scores only in TRG in group comparisons ($p < 0.01$). No significant difference was found in any of the comparisons between groups ($p > 0.05$).

Strength-Proprioception

Objective muscle strength and joint proprioception measurement values are given in Table 3. Except for the left hamstring strength values, there was a significant improvement in TRG within the group in other values ($p < 0.01$). In intragroup comparisons, considerable progress was found in CRG in other values except for right quadriceps femoris muscle strength ($p < 0.05$). In the intergroup comparison, a more significant improvement in right hamstring muscle strength was found in TRG after treatment ($p < 0.05$). The corrected analysis showed a significant difference in favor of TRG in the right quadriceps femoris muscle strength ($p < 0.01$). There was no significant difference between the groups in other muscle strength measurements ($p > 0.05$).

Significant improvements in proprioception measures were reported within groups ($p < 0.01$). Only right extremity proprioception showed no significant improvement in CRG ($p > 0.05$). In comparisons between groups in proprioception measurements, a more significant decrease in TRG was found on both sides ($p < 0.05$).

Motivation-Satisfaction-Usability

EARS and TSUQ values are given in Table 4. TRG showed significantly greater motivation and exercise adherence for EARS between the groups ($p < 0.01$). When TSUQ values were analyzed in TRG, the median value was 87. More than half (52%) of the participants in TRG scored above the median.

Table 1. Demographic and clinical characteristics of the participants

	Telerehabilitation (n=25)	Standard rehabilitation (n=24)	p
Gender (female/male, %)	44/56	58.3/41.7	0.316 ^a
Age (years, mean±SD)	38.36±9.84	43.91±9.1	0.062 ^b
BMI (kg/m ² , mean±SD)	27.13±5.4	26.94±4.09	0.895 ^c
Living area (urban/rural, %)	88/12	70.8/29.2	0.171 ^d
Education status (primary/high school and above, %)	24/76	37.5/62.5	0.305 ^a
Working status (working/not working, %)	68/32	54.2/45.8	0.320 ^a
Smoking (yes/no, %)	32/68	29.2/70.8	0.830 ^a
Presence of chronic disease (present/absent, %)	24/76	29.2/70.8	0.682 ^a
Symptom duration (months, mean±SD)	16.56±18.25	11.7±12.58	0.208 ^b
Affected side (right/left, %)	52/48	62.5/37.5	0.458 ^a

n: the number of participants, SD: standard deviation, BMI: body mass index, kg: kilogram, m: metre, a: Pearson Chi-Square test, b: Mann-Whitney U test, c: independent sample t test, d: Fisher's Exact test

Table 2. Patient self-reported outcome measures between and within groups

	Telerehabilitation (n=25)	Standard rehabilitation (n=24)	P (between group)	
r-VAS*	Before treatment (mean±SD)	3.66±2.48	2.64±1.91	0.16 ^a
	After treatment (mean±SD)	2.1±1.96	1.95±2.01	0.773 ^a
	Δ (mean)	-1.56	-0.68	0.089 ^a
	p (within group)	0.000473^b	0.008^b	
a-VAS*	Before treatment (mean±SD)	7.42±1.92	6.47±1.67	0.054 ^a
	After treatment (mean±SD)	4.78±1.84	4.75±2.15	0.808 ^a
	Δ (mean)	-2.64	-1.72	0.03^a
	p (within group)	0.000049^b	0.000088^b	
WOMAC-pain*	Before treatment (mean±SD)	39±16.58	30.62±19.24	0.115 ^a
	After treatment (mean±SD)	25±16.61	24.16±21.45	0.546 ^a
	Δ (mean)	-14	-6.45	0.07 ^a
	p (within group)	0.0001^b	0.002^b	
WOMAC-stiffness*	Before treatment (mean±SD)	25±17.67	23.43±19.61	0.838 ^a
	After treatment (mean±SD)	11±15.44	15.1±17.28	0.370 ^a
	Δ (mean)	-14	-8.33	0.109 ^a
	p (within group)	0.001^b	0.001^b	
WOMAC-function*	Before treatment (mean±SD)	31.64±16.43	33.32±19.78	0.711 ^a
	After treatment (mean±SD)	24.28±14.73	29.63±23.35	0.787 ^a
	Δ (mean)	-7.35	-3.69	0.352 ^a
	p (within group)	0.004^b	0.002^b	
WOMAC-total*	Before treatment (mean±SD)	32.62±15.4	31.94±18.85	0.992 ^a
	After treatment (mean±SD)	23.32±14.3	27.68±22.92	0.795 ^a
	Δ (mean)	-9.29	-4.25	0.161 ^a
	p (within group)	0.001^b	0.003^b	
SF-12 PCS**	Before treatment (mean±SD)	35.27±8.1	38.44±9.78	0.223 ^d
	After treatment (mean±SD)	39.75±6.92	40.65±10.07	0.716 ^d
	Δ (mean)	4.47	2.21	0.246 ^a
	p (within group)	0.005^c	0.142 ^c	
SF-12 MCS**	Before treatment (mean±SD)	39.97±10.41	39.29±10.41	0.697 ^a
	After treatment (mean±SD)	46.27±8.67	42.81±9.43	0.197 ^a
	Δ (mean)	6.3	3.52	0.254 ^a
	p (within group)	0.008^b	0.067 ^b	

n: the number of participants, SD: standard deviation, Δ: mean difference, r-VAS: Visual Analog Scale for rest, a-VAS: Visual Analog Scale for activity, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, SF-12 PCS: short form 12 physical component summary, SF-12 MCS: short form 12 mental component summary, a: Mann-Whitney U test, b: Wilcoxon signed-rank test, c: Paired t test, d: independent sample t test, *: Lower values=Better, **: Higher values=Better

Table 3. Objective measurement scores between and within groups

		Telerehabilitation (n=25)	Standard rehabilitation (n=24)	P (between group)
HHD-QF right extremity**	Before treatment (kg, mean±SD)	21.73±7.64	22.64±5.96	0.645 ^a
	After treatment (kg, mean±SD)	24.59±6.86	23.86±5.96	0.695 ^a
	Δ (mean)	2.85	1.21	0.007^d
	p (within group)	0.002^b	0.062 ^b	
HHD-QF left extremity**	Before treatment (kg, mean±SD)	22.27±7	22.83±6.18	0.769 ^a
	After treatment (kg, mean±SD)	25.58±6.86	25.25±5.42	0.851 ^a
	Δ (mean)	3.3	2.41	0.285 ^d
	p (within group)	0.005^b	0.00004^c	
HHD-H right extremity**	Before treatment (kg, mean±SD)	13.97±4.7	11.7±4.62	0.095 ^a
	After treatment (kg, mean±SD)	15.35±5.28	12.4±4.66	0.035 ^a
	Δ (mean)	1.38	0.7	0.435 ^d
	p (within group)	0.003^c	0.016^c	
HHD-H left extremity**	Before treatment (kg, mean±SD)	13.28±4.53	11.41±4.48	0.171 ^d
	After treatment (kg, mean±SD)	14.62±4.97	12.35±4.71	0.136 ^d
	Δ (mean)	1.33	0.93	0.638 ^d
	p (within group)	0.052 ^b	0.002^b	
Proprioception right extremity*	Before treatment (°, mean±SD)	4.29±2.28	5.01±4.04	0.984 ^d
	After treatment (°, mean±SD)	2.42±1.21	4.14±2.83	0.042^d
	Δ (mean)	-1.86	-0.86	0.024^d
	p (within group)	0.000319^c	0.217 ^c	
Proprioception left extremity*	Before treatment (°, mean±SD)	7.83±3.73	6.49±3.66	0.211 ^a
	After treatment (°, mean±SD)	3.21±1.64	4.33±1.96	0.035^a
	Δ (mean)	-4.62	-2.16	0.01^d
	p (within group)	0.000018^c	0.005^b	

n: the number of participants, kg: kilogram, °: degree, SD: standard deviation, Δ: mean difference, HHD-QF: Hand Held Dynamometer Quadriceps Femoris muscle measurement, HHD-H: Hand Held Dynamometer Hamstring muscle measurement, a: independent sample t test, b: paired t test, c: Wilcoxon signed-rank test, d: Mann-Whitney U test, *: lower values=better, **: higher values=better

Table 4. Changes in motivation, satisfaction between and within the groups

		Telerehabilitation (n=25)	Standard rehabilitation (n=24)	p (between group)
EARS**	After treatment (mean±SD)	15.44±4.26	10.62±5.53	0.004^a
TSUQ**	Post-treatment (median)	87		
	Below the median value (n/%)	12/48		
	Median value and above (n/%)	13/52		

n: the number of participants, SD: standard deviation, EARS: exercise adherence rating scale, TSUQ: telemedicine satisfaction and usefulness questionnaire, a: Mann-Whitney U test, **: higher values=better

DISCUSSION

The present study aimed to evaluate the effect of telehealth-based rehabilitation on patient-reported outcomes and objective clinical measurements in individuals with degenerative meniscal tears. Our research showed that telerehabilitation did not provide an additional advantage in subjective parameters (rest-VAS, WOMAC, and SF-12) assessing pain, function, and quality of life. However, in objective measurements, it was observed that the telehealth-based exercise group improved more in activity pain, quadriceps femoris, hamstring muscle strength and proprioception sense. Finally, it was observed that the participation and satisfaction of individuals who received telerehabilitation were higher.

The clinical benefits and cost-satisfaction advantages of remote rehabilitation applications were widely known (26,27). The effectiveness of the exercise program with telehealth in knee osteoarthritis and total knee arthroplasty groups has been demonstrated (26,28). However, no other studies have shown the effectiveness of telerehabilitation in individuals with degenerative meniscal tears. Our study provided an additional opportunity to observe the achievements of telemedicine in terms of patient-based and objective measurements. Because sometimes, clinical improvements are only observed with objective measurement results (29). Patients' statements regarding their symptoms may not reflect the actual outcomes. Since monitoring changes in parameters such as pain and

quality of life are associated with psychosocial status, it suggests the importance of considering objective and subjective evaluation parameters together (30). Indeed, the results of our study showed that telerehabilitation did not provide an additional advantage in subjective parameters (rest-VAS, WOMAC, and SF-12) assessing pain, function, and quality of life. However, in objective measurements, it was observed that the telehealth-based exercise group improved more in activity pain, quadriceps femoris, hamstring muscle strength, and proprioception sense. Finally, it was observed that the participation and satisfaction of individuals who received telerehabilitation were higher. It can be communicated that the additional advancements obtained from the 8-week exercise program in the telerehabilitation group were reflected in the clinician-based measurements but not in the individual rest-pain, function, and quality of life reports, despite the increased participation and satisfaction. Strength and proprioception gains achieved in dynamometer and goniometer-based measurements may not have been achieved as functional gains due to the lack of improvement in pain and, therefore, may not have contributed positively to the physical and psychological components of quality of life.

There were significant improvements in both groups in terms of rest pain. However, there was no difference between groups. This result showed that increased participation and satisfaction with telerehabilitation were more beneficial for strength-proprioseption gains than pain. A comprehensive systematic review showed that most studies did not emphasize any additional advantage of telerehabilitation on pain (31). It may be advantageous to include education-based pain management with a fear-avoidance model or cognitive behavioral therapy to provide more advancements with telerehabilitation in terms of pain (30,32). A similar study also emphasized the superiority of a training program that promotes physical activity and exercise for individuals with knee osteoarthritis (33).

The superiority of telerehabilitation was not demonstrated in pain and function parameters evaluated with WOMAC. No functional gain might be related to the patient's pain levels. Although it was observed that the patients in the telerehabilitation group improved muscle strength and proprioception, it demonstrates the importance of pain in functional gain. A large meta-analysis has shown that telerehabilitation is more effective in pain and functional gain among post-arthroplasty cases (34). However, these studies include older individuals with more disabilities, where improvements are essential even in basic daily activities. In our research, it was inconceivable to achieve functional gains on WOMAC regarding the relatively young sample. Because WOMAC is a PROM that evaluates disability in older individuals, especially those containing basic and instrumental daily living activities (19,35). In this respect, conducting the study with more specific PROMs would provide indications for future studies.

There was no difference between the two groups in terms of SF-12 results. It should be emphasized that quality of life is a more suitable parameter for longer-term gains.

The effect of symptomatic gains on quality of life can be considered in the longer term. Telerehabilitation did not provide an additional advantage regarding the quality of life in individuals with knee osteoarthritis with more advanced symptoms, which is the closest case group (36). Moreover, it should be emphasized that these results are in parallel with our results since they include quality-of-life findings, including a 6-month follow-up. In addition, telerehabilitation was not found to be more effective in quality of life in individuals with total knee arthroplasty compared to the conventional program (37).

Our study demonstrated an additional advantage of telerehabilitation regarding clinician-based strength and proprioception measurements. Among these measurements, it was observed that more improvements were recorded in the right extremity quadriceps femoris and hamstring and both extremity proprioception measurements. A recent randomized controlled study focused on the advantage of virtual reality-based telerehabilitation in proprioception in individuals with total knee arthroplasty (38). In this context, the fact the exercises such as "mini squats", which are included in our exercise program in the current case group, where proprioceptive losses are likely to occur through meniscus degeneration, contain more basic multimedia narration with video and in this respect, more learnable for patients, may have provided more gains in a proprioceptive sense. Finally, a study similar to our hamstring and quadriceps gains has been shown in the literature in individuals with total knee arthroplasty (34,39). The fact that telerehabilitation provides more advantages in quadriceps muscle strength may have been achieved through the video advantage of telerehabilitation, especially in exercises where strengthening is more effective by waiting for a specific time in certain positions. An objective pain assessment may be possible with an algometer. In this respect, a subjective measurement parameter evaluated with VAS in PROMs can be compared with the objective.

Limitations

Some limitations of the study should be mentioned. The first is the absence of evaluator blindness. This situation brings to mind the possibility of bias risk, according to PEDro and Cochrane (40). In this respect, performing objective measurement results by a single blind evaluator can minimize the risk of measurement error or bias. However, the available facilities did not allow blinding in this trial. Second, individuals are evaluated with less specific meniscus assessment PROMs rather than WOMAC and VAS. This situation was due to the need for more Turkish standardized assessment tools. Finally, the clinical comparison could only be constructed with knee osteoarthritis and arthroplasty groups, as there were no other studies on the effectiveness of telerehabilitation in the meniscus. However, considering the significant difference in disability and mean age distribution of individuals, this showed that the clinical features of each case group were suitable for a stratified comparison.

CONCLUSION

Our study showed that telerehabilitation did not provide an additional advantage in subjective parameters (rest-VAS, WOMAC, and SF-12) evaluating pain, function, and quality of life. However, in objective measurements, it was observed that the remote rehabilitation group improved more in activity pain, quadriceps femoris, hamstring muscle strength, and proprioception sense. Finally, as expected, it was observed that the participation and satisfaction of individuals who received telerehabilitation were higher. It can be said that the additional gains obtained from the 8-week exercise program in the telerehabilitation group were reflected in the clinician-based measurements but not in the rest pain, function, and quality of life reports, despite the increased participation and satisfaction.

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Conflict of interest: The authors have no conflicts of interest to declare.

Ethical approval: The study was carried out in accordance with the ethical principles and the Helsinki Declaration. Informed consent of the patients was obtained. The study protocol was approved by the ethics committee of Muğla Sıtkı Koçman University (Decision dated 05/01/2022 and numbered 1/IV). The study protocol was registered (ClinicalTrials.gov Identifier: NCT05233839).

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REFERENCES

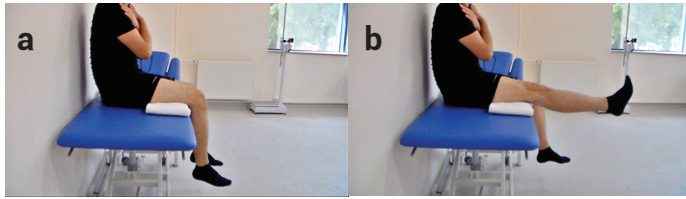
1. Beaufils P, Becker R, Kopf S, et al. Surgical management of degenerative meniscus lesions: the 2016 ESSKA meniscus consensus. *Knee Surg Sports Traumatol Arthrosc.* 2017;25:335-346.
2. Englund M, Felson DT, Guermazi A, et al. Risk factors for medial meniscal pathology on knee MRI in older US adults: a multicentre prospective cohort study. *Ann Rheum Dis.* 2011;70:1733-9.
3. Swart NM, van Oudenaarde K, Reijnierse M, et al. Effectiveness of exercise therapy for meniscal lesions in adults: a systematic review and meta-analysis. *J Sci Med Sport.* 2016;19:990-8.
4. Essilfie A, Kang HP, Mayer EN, et al. Are orthopaedic surgeons performing fewer arthroscopic partial meniscectomies in patients greater than 50 years old? a national database study. *Arthroscopy.* 2019;35:1152-9.e1.
5. Giuffrida A, Di Bari A, Falzone E, et al. Conservative vs. surgical approach for degenerative meniscal injuries: a systematic review of clinical evidence. *Eur Rev Med Pharmacol Sci.* 2020;24:2874-85.
6. Stensrud S, Roos EM, Risberg MA. A 12-week exercise therapy program in middle-aged patients with degenerative meniscus tears: a case series with 1-year follow-up. *J Orthop Sports Phys Ther.* 2012;42:919-31.
7. Skou ST, Thorlund JB. A 12-week supervised exercise therapy program for young adults with a meniscal tear: Program development and feasibility study. *J Bodyw Mov Ther.* 2018;22:786-91.
8. Tuakli-Wosornu YA, Selzer F, Losina E, Katz JN. Predictors of Exercise Adherence in Patients With Meniscal Tear and Osteoarthritis. *Arch Phys Med Rehabil.* 2016;97:1945-52.
9. Katz NB, Tenforde AS. Chapter 14 - Telerehabilitation for Musculoskeletal Injuries. In: Alexander M, ed. *Telerehabilitation.* New Delhi: Elsevier. 2022;197-212.
10. Gilbert AW, Jaggi A, May CR. What is the patient acceptability of real time 1:1 videoconferencing in an orthopaedics setting? a systematic review. *Physiotherapy.* 2018;104:178-86.
11. McCue M, Fairman A, Pramuka M. Enhancing quality of life through telerehabilitation. *Phys Med Rehabil Clin N Am.* 2010;21:195-205.
12. Cottrell MA, Galea OA, O'Leary SP, et al. Real-time telerehabilitation for the treatment of musculoskeletal conditions is effective and comparable to standard practice: a systematic review and meta-analysis. *Clin Rehabil.* 2016;31:625-38.
13. Richardson BR, Truter P, Blumke R, Russell TG. Physiotherapy assessment and diagnosis of musculoskeletal disorders of the knee via telerehabilitation. *J Telemed Telecare.* 2016;23:88-95.
14. Herrero CP, Bloom DA, Lin CC, et al. Patient satisfaction is equivalent using telemedicine versus office-based follow-up after arthroscopic meniscal surgery: a prospective, randomized controlled trial. *J Bone Joint Surg Am.* 2021;103:771-7.
15. Liu X, Faes L, Calvert MJ, Denniston AK. Extension of the CONSORT and SPIRIT statements. *Lancet.* 2019;394:1225.
16. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods.* 2007;39:175-91.
17. Özden F, Sari Z, Karaman ÖN, Aydoğmuş H. The effect of video exercise-based telerehabilitation on clinical outcomes, expectation, satisfaction, and motivation in patients with chronic low back pain. *Ir J Med Sci.* 2022;191:1229-39.
18. Moses MJ, Tishelman JC, Stekas N, et al. Comparison of patient reported outcome measurement information system with neck disability index and visual analog scale in patients with neck pain. *Spine.* 2019;44: E162-7.
19. Tüzün EH, Eker L, Aytar A, et al. Acceptability, reliability, validity and responsiveness of the Turkish version of WOMAC osteoarthritis index. *Osteoarthritis Cartilage.* 2005;13:28-33.
20. Suner-Keklik S, Cobanoğlu-Seven G, Kafa N, et al. The validity and reliability of knee proprioception measurement performed with inclinometer in different positions. *J Sport Rehabil.* 2017;26.
21. Ribeiro F, Venâncio J, Quintas P, Oliveira J. The effect of fatigue on knee position sense is not dependent upon the muscle group fatigued. *Muscle Nerve.* 2011;44:217-20.
22. Bohannon RW, Kindig J, Sabo G, et al. Isometric knee

- extension force measured using a handheld dynamometer with and without belt-stabilization. *Physiother Theory Pract.* 2012;28:562-8.
23. Newman-Beinart NA, Norton S, Dowling D, et al. The development and initial psychometric evaluation of a measure assessing adherence to prescribed exercise: the Exercise Adherence Rating Scale (EARS). *Physiotherapy.* 2017;103:180-5.
 24. Soyulu C, Kütük B. Reliability and validity of the Turkish version of SF-12 health survey. *Turk Psikiyatri Derg.* 2022;33:108-17.
 25. Özkeskin M, Özden F, Ekmekçi Ö, Yüceyar N. The reliability and validity of the Turkish version of the Telemedicine Satisfaction and Usefulness Questionnaire (TSUQ) and Telemedicine Patient Questionnaire (TPQ) in individuals with multiple sclerosis. *Neurol Sci.* 2022;43:1921-7.
 26. Yang Y, Li S, Cai Y, et al. Effectiveness of telehealth-based exercise interventions on pain, physical function and quality of life in patients with knee osteoarthritis: a meta-analysis. *J Clin Nurs.* 2023;32:2505-20.
 27. Rennie K, Taylor C, Corriero AC, et al. The current accuracy, cost-effectiveness, and uses of musculoskeletal telehealth and telerehabilitation services. *Curr Sports Med Rep.* 2022;21:247-60.
 28. Shukla H, Nair S, Thakker D. Role of telerehabilitation in patients following total knee arthroplasty: evidence from a systematic literature review and meta-analysis. *J Telemed Telecare.* 2017;23:339-46.
 29. Özden F, Karaman ÖN, Tuğay N, et al. The relationship of radiographic findings with pain, function, and quality of life in patients with knee osteoarthritis. *J Clin Orthop Trauma.* 2020;11:S512-S7.
 30. Leeuw M, Goossens ME, Linton SJ, et al. The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. *J Behav Med.* 2007;30:77-94.
 31. McHugh C, Kostic A, Katz J, Losina E. Effectiveness of remote exercise programs in reducing pain for patients with knee osteoarthritis: A systematic review of randomized trials. *Osteoarthr Cartil Open.* 2022;4:100264.
 32. Rothbaum BO, Meadows EA, Resick P, Foy DW. Cognitive-behavioral therapy. In: Foa EB, Keane TM, Friedman MJ, eds, *Effective treatments for PTSD: Practice guidelines from the International Society for Traumatic Stress Studies.* New York: The Guilford Press. 2000;320-5.
 33. Jones SE, Campbell PK, Kimp AJ, et al. Evaluation of a novel e-learning program for physiotherapists to manage knee osteoarthritis via telehealth: qualitative study nested in the PEAK (physiotherapy exercise and physical activity for knee osteoarthritis) randomized controlled trial. *J Med Internet Res.* 2021;23:e25872.
 34. Jiang S, Xiang J, Gao X, et al. The comparison of telerehabilitation and face-to-face rehabilitation after total knee arthroplasty: a systematic review and meta-analysis. *J Telemed Telecare.* 2018;24:257-62.
 35. Roos EM, Roos HP, Lohmander LS. WOMAC Osteoarthritis Index—additional dimensions for use in subjects with post-traumatic osteoarthritis of the knee. *Osteoarthritis Cartilage.* 1999;7:216-21.
 36. Azma K, RezaSoltani Z, Rezaeimoghaddam F, et al. Efficacy of tele-rehabilitation compared with office-based physical therapy in patients with knee osteoarthritis: a randomized clinical trial. *J Telemed Telecare.* 2018;24:560-5.
 37. Russell TG, Buttrum P, Wootton R, Jull GA. Internet-based outpatient telerehabilitation for patients following total knee arthroplasty: a randomized controlled trial. *J Bone Joint Surg Am.* 2011;93:113-20.
 38. Gianola S, Stucovitz E, Castellini G, et al. Effects of early virtual reality-based rehabilitation in patients with total knee arthroplasty: a randomized controlled trial. *Medicine.* 2020;99:e19136.
 39. An J, Ryu H-K, Lyu S-J, et al. Effects of preoperative telerehabilitation on muscle strength, range of motion, and functional outcomes in candidates for total knee arthroplasty: a single-blind randomized controlled trial. *Int J Environ Res Public Health.* 2021;18:6071.
 40. Armijo-Olivo S, da Costa BR, Cummings GG, et al. PEDro or Cochrane to assess the quality of clinical trials? A meta-epidemiological study. *PloS One.* 2015;10:e0132634.

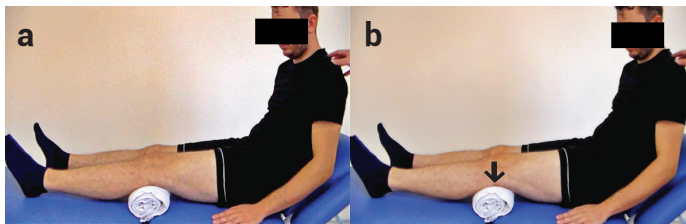
Additional File 1

Home Exercises

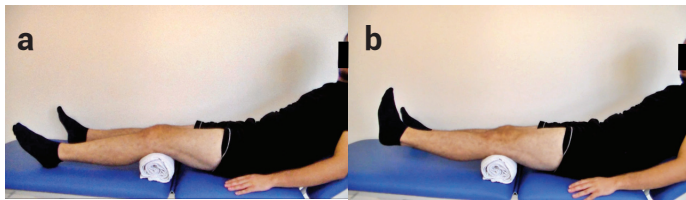
Exercise 1: Knee extension in sitting position



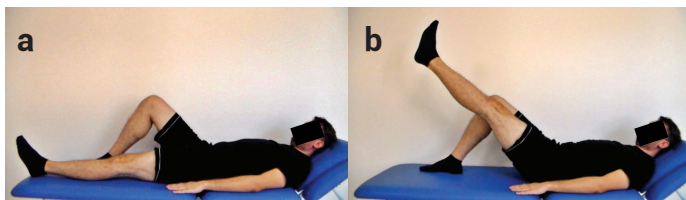
Exercise 2: Isometric knee extension with towel compression below the knee in the long sitting position



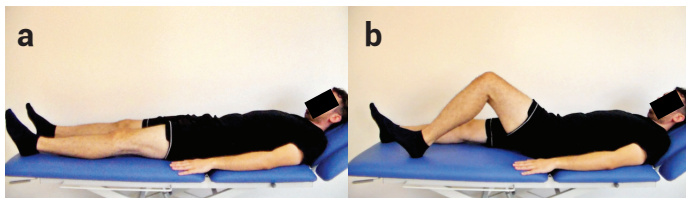
Exercise 3: Terminal knee extension in long sitting position



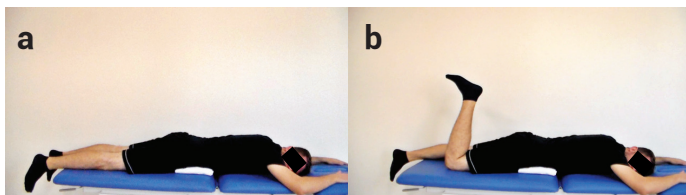
Exercise 4: Straight leg raise in supine position



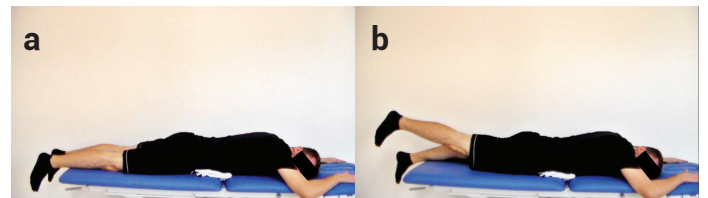
Exercise 5: Heel shift in supine position



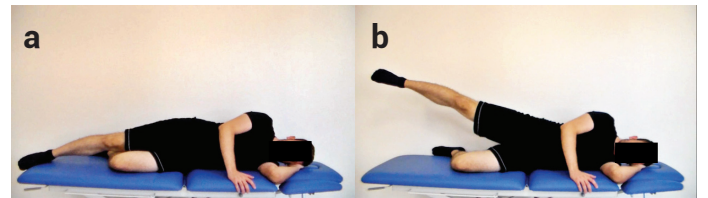
Exercise 6: 90° knee flexion in prone position



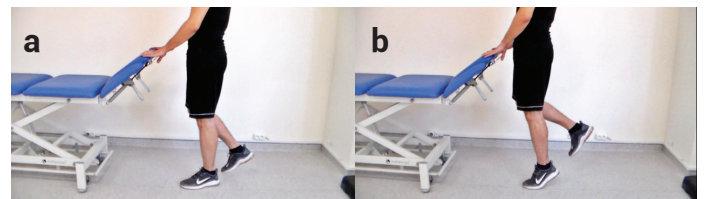
Exercise 7: Hip extension with knee extended in prone position



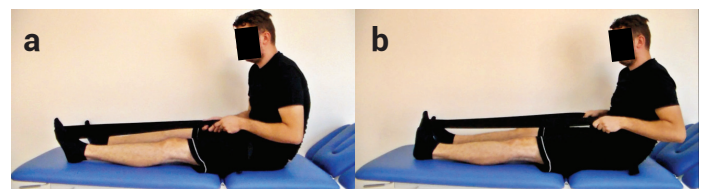
Exercise 8: Hip abduction in side lying position



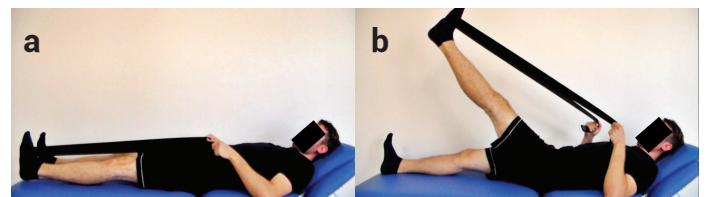
Exercise 9: Standing toe raise



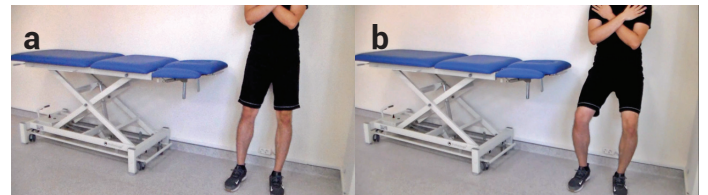
Exercise 10: Gastrosoleus stretching with rigid sheet in long sitting position



Exercise 11: Hamstring stretching with rigid sheet in supine position



Exercise 12: Half squat with sliding back on wall



Additional File 2

Useful Suggestions for Knee Pain

1. Go up and down as few stairs as possible and use the elevator if available.
2. Avoid activities such as crossing legs, tucking legs under, and sitting on the floor. Choose a seat that is a high chair or sofa. Do not sit on low and soft sofas. When sitting, put your feet a little forward and try not to bend your knees too much. When standing up after sitting, try to get support from somewhere with your hands.
3. Sit on a stool when praying.
4. When using the toilet, use a European (sitting) toilet. Do not use squat toilets.
5. If you are overweight, consult a specialist to lose weight and do the exercises we recommend regularly. Excess weight puts excessive strain on your knee joint and causes further wear on your joint surfaces. So be careful about losing weight.
6. Do not stand still for long periods of time. If you are in a situation where you have to stand for a long time, if there is a small elevation where you are every 5 minutes, put your feet on that elevation in order to let your knees rest. If there is no elevation, bend one leg slightly from the knee and rest that knee. Or, with a cane, you can move the cane to the right and left side by side, allowing your knees to rest.
7. If you are a smoker, stop smoking. Smoking and cigarette smoke will adversely affect blood circulation and prevent adequate nutrition of your knee joint. As a result, the healing of your knee will really slow down.
8. When you have knee pain, place a cold pack wrapped in a towel on your knee for 5 minutes. Meanwhile, breathe calmly into your lower abdomen for 4 seconds and exhale slowly for 8 seconds. Get rid of bad thoughts, do an activity such as listening to calming music, drinking tea, watching beautiful scenery, thinking about a good moment.
9. Do not do movements that cause pain in your knee. When your pain starts, take a break from your work and rest for a while.
10. Do not walk for a long time. Walks should not exceed 15-20 minutes. If you have to walk for a long time, walk with a cane on the painless side. Use soft-soled shoes. The ground you walk on should be soft ground suitable for walking. Do not walk on extremely rough roads.
11. Do the recommended exercises regularly. These exercises will strengthen your muscles, accelerate nutrition and healing of your knee joint, and make you feel more energetic.
12. Remember, the only treatment for your knee pain before surgery and without adverse effects is regular exercise and following the recommendations.

We wish you good health.



Examination of Age and Gender-Related Changes in Spinopelvic Parameters in Children and Adolescents Using Computed Tomography Images

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Abstract

Aim: In order for a person to stand in a balanced way, the pelvis and spine must be in harmony. The aim of this study was to determine the normal ranges of spinopelvic parameters in children and adolescents in Türkiye.

Material and Method: In our study, computed tomography images of 1018 healthy 7-17 year olds were examined. As a result of this examination, sacrum pubic incidence, lumbar lordosis, sacral slope, sacral kyphosis, pelvic tilt and pelvic incidence were measured.

Results: The sacrum pubic incidence was $58.71 \pm 6.17^\circ$, sacral slope 37.26 ± 5.77 , lumbar lordosis $42.98 \pm 8.06^\circ$, sacral kyphosis $21.27 \pm 9.96^\circ$, pelvic incidence 46.77 ± 6.38 , and pelvic tilt $9.51 \pm 5.06^\circ$. The calculations revealed that, with age, all parameters except pelvic tilt increased significantly. A statistically significant difference was found between the age groups.

Conclusion: The results of this study will contribute to the existing literature and may give clinicians insight into sagittal corrections in spine and pelvic surgery.

Keywords: Sagittal balance, spinopelvic parameters, sacral slope, pelvic incidence

INTRODUCTION

In recent years, numerous studies have emphasized the significance of pelvis morphology in balanced walking and standing upright (1-4). Understanding the morphology of the pelvis in healthy individuals provides important information for planned surgery operations for patients with spinal deformity.

The spine and pelvis must be delicately balanced in order to maintain a proper standing posture. The spine and pelvis, which are lined up to provide the least energy consumption, will also provide a balanced posture (5).

Basic parameters used in the evaluation of spinopelvic balance are sacral slope (SS), pelvic tilt (PT) and pelvic incidence. Pelvic incidence (PI) is often used to assess the sagittal balance of the spine because It is a constant

parameter unaffected by the pelvic and spine's positions (6). In hip osteoarthritis or when the femoral head is not spherical, two new parameters have been proposed, namely sacrum pubic posterior angle and sacrum pubic incidence, to replace pelvic incidence (7).

Numerous studies have shown a significant relationship between spinal sagittal balance and pelvic parameters, particularly sacral kyphosis (SK) and lumbar lordosis (LL). It is necessary to consider the spine and pelvis as a whole (8-11).

The presence of abnormal spinopelvic parameters are lumbar disc hernia, low back pain, degenerative and isthmic spondylolisthesis, degenerative disc disease, hip osteoarthritis and similar pathologies affect the formation and progression. In patients with deformity, spinopelvic parameters fall outside the normal range (12).

CITATION

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Spinopelvic parameters normative values by age groups and population have been reported in numerous research (13-17). However, there have been few studies conducted on the Turkish population of children and adolescents, and these studies have utilized lateral radiography. No study has been found regarding 3D computed tomography (CT) images.

This study aims to determine the normative ranges of spinopelvic parameters using 3D CT images and to examine the development of these parameters in the Turkish child and adolescent population.

MATERIAL AND METHOD

This study was carried out with the scope of the approval and information of Erciyes University Clinical Research Ethics Committee (Date and Decision No: 2019/587).

In this study, pelvis-abdominal CT images taken for any indication of the Turkish population aged 7-17 years were examined. After the examination, individuals with pelvic trauma, hip dislocation, vertebral fracture and scoliosis were excluded and 1018 pelvis-abdominal CT images were selected. The study examined pelvis-abdominal CT images of 1018 healthy children and adolescents (503 female, 515 male, aged 7-17 years) from the Turkish population. The study measured sacral kyphosis, lumbar lordosis, sacral slope, pelvic tilt, pelvic incidence and sacrum pubic incidence (SPI). Each age range is regarded as a group when evaluating by age and divided into 11 groups. The differences between the groups were evaluated statistically.

Creation of 3D Pelvis Skeleton and Measurement of Angles

Three-dimensional pelvis skeleton model was created from pelvis-abdomen CT images for 3D measurement. From this model, anatomical structures other than the reference points required for measurement were excluded from this skeleton model. The measurement of the parameters was performed on the sagittal plane through this image.

While measuring the sacral slope, pelvic tilt and pelvic incidence, the wings of the sacrum and femoral heads were adjusted on top of the sagittal plane. Then, the screen shot was taken and the measurement of the parameters was carried out in the ImageJ program with the Duval-Beaupère method (Figure 1) (6).

Lumbar lordosis and sacral kyphosis were measured using Picture Archiving and Communication System (PACS). In the lumbar lordosis measurement using the Cobb method, the angle between the line drawn tangent to the superior endplate of L1 and the line drawn tangent to the superior endplate of S1 was calculated (8). Sacral kyphosis is defined as the angle formed by a line connecting the midpoint of the inferior and superior borders of S1 and a line connecting the inferior borders of S2 and S4. (Figure 2) (9,18).

While measuring the SPI, the sacrum wings were adjusted to overlap and the created pelvic skeleton was cut in half in a horizontal plane. The left part was removed and the sacrum pubic incidence was measured in the ImageJ program through this image. To measure the sacrum pubic incidence, the vertical line passing through the midpoint between the anterior and posterior edges of the upper surface of S1 and the angle between this point and the line connecting the upper edge of the symphysis pubis are measured (Figure 1) (7).

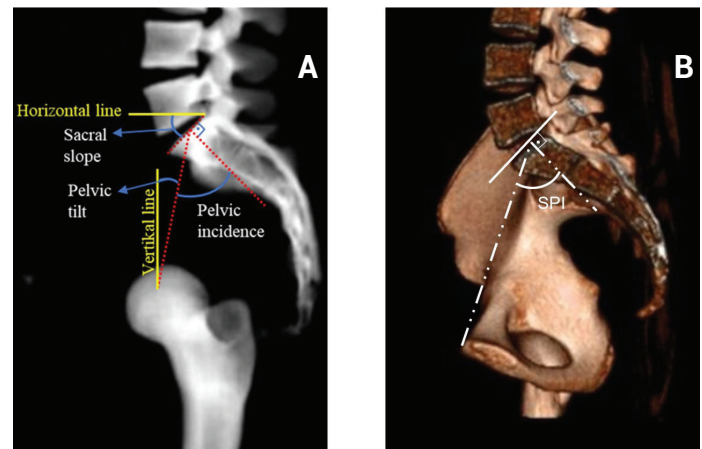


Figure 1. 1A. Measurement of PI, PT and SS with the Duval-Beaupère method. In PI measurement, the midpoint of the superior endplate of S1 is determined and a perpendicular line is drawn from this point. Then, a line is drawn from this determined point to the femoral head. The angle between this line and the vertical line gives the pelvic incidence. In PT measurement, the angle created by a vertical line that passes through the sacral endplate's midpoint, the center of the femoral axis, and the center of the femoral head is measured. In SS measurement, the angle between the line tangent to the superior endplate of S1 and the horizontal line passing through the rear point of the superior endplate of S1 is measured. 1B. In SPI measurement, the vertical line passing through the midpoint between the anterior and posterior edges of the superior endplate of S1 and the angle between this point and the line connecting the upper edge of the symphysis pubis is measured.

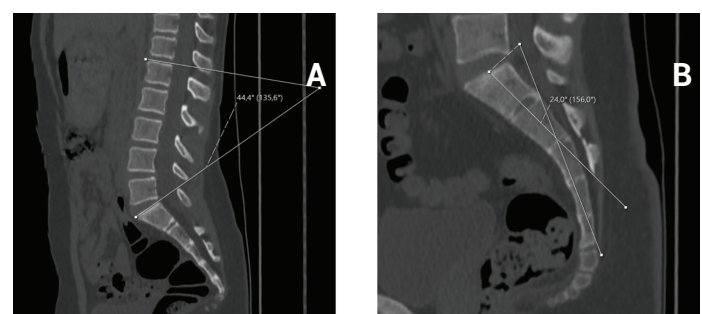


Figure 2. 2A. Measurement of lumbar lordosis by the Cobb method, in the LL measurement, the angle between the line drawn tangent to the upper surface of L1 and the line drawn tangent to the upper surface of S1 was measured. 2B. In SC measurement, the angle formed by the midpoint of the inferior and superior borders of S1 and the line connecting the inferior borders of S2 and S4 was measured.

Statistical Analysis

The normal distribution suitability of the data was assessed using histograms, Q-Q plots, and the Shapiro-Wilk test. Levene's test was used to test for variance homogeneity. For quantitative variables, two independent

samples t-tests were used to compare groups. Method comparisons were performed using Passing-Bablok regression analysis. The statistical software TURCOSA (Turcosa Analytical Solutions Ltd. Co., www.turcosa.com.tr) was used for data analysis. The significance level was set at $p < 0.05$.

Correlation coefficient levels: $0.0 \leq r < 0.20$ very poor relationship, $0.20 < r < 0.40$ weak level relationship, $0.40 < r < 0.60$ medium level relationship, $0.60 \leq r < 0.80$ good level relationship, $0.80 \leq r < 1.00$ very good relationship.

RESULTS

Comparison of Spinopelvic Parameters by Gender

PI, PT, SS, LL, SK and SPI values of 1018 (503 female, 515 male) healthy individuals included in the study were measured. Table 1 shows the mean values and standard deviations of the spinopelvic parameters for males and females. The LL value was higher in women than in men and this statistical difference was significant ($p < 0.01$). PI, PT, SS, SK and SPI values were not statistically significant in men and women ($p > 0.05$).

Table 1. Comparison of spinopelvic parameters by gender

Parameters	Gender		p value
	Female (n=503)	Male (n=515)	
PI (°)	47.03±6.68	46.52±6.07	0.202
PT (°)	9.49±5.21	9.54±4.91	0.873
SS (°)	37.54±5.93	36.98±5.60	0.120
LL (°)	43.97±8.41	42.01±7.58	<0.01*
SK (°)	21.44±10.06	21.10±9.88	0.583
SPI (°)	58.9±6.50	58.54±5.84	0.350

Data are shown as mean±standard deviation. PI: pelvic incidence, PT: pelvic tilt, SS: sacral slope, LL: lumbar lordosis, SK: sacral kyphosis, SPI: sacrum pubic incidence

Values of Spinopelvic Parameters

Table 2 presents the measured spinopelvic parameters results. The PI, PT, SS, LL, SK and SPI means (\pm standard deviation) were $46.77 \pm 6.38^\circ$, $9.51 \pm 5.06^\circ$, $37.26 \pm 5.77^\circ$, $42.98 \pm 8.06^\circ$, $21.27 \pm 9.96^\circ$ and $58.71 \pm 6.17^\circ$ respectively. PI, SS, LL, SK and SPI tend to increase with age. This increase in PI and SPI becomes particularly evident with the onset

of puberty (Figure 3). The PI value shows a statistically significant difference between the 7-11 and 13-17 age groups and between the 12 and 15-17 age groups ($p < 0.01$). SS and SPI values show statistically significant differences between 7-9 and 13-17 age groups ($p < 0.01$). Age-related changes and statistical significance of spinopelvic parameters are shown in Figure 3.

Table 2. Values of spinopelvic parameters

Age	n	PI (°)	PT (°)	SS (°)	LL (°)	SK (°)	SPI (°)
7	83	44.08±5.47	10.43±5.56	33.64±6.24	38.65±7.13	16.33±7.93	55.78±5.20
8	96	43.73±5.81	8.77±5.67	34.96±5.26	41.25±8.30	18.90±8.38	56.07±5.60
9	84	43.45±5.14	8.38±5.11	35.07±5.59	42.29±8.16	21.33±9.09	55.51±5.27
10	85	44.64±6.40	8.20±5.48	36.44±5.24	42.46±7.57	20.65±8.56	56.73±6.22
11	85	44.61±6.51	8.47±5.45	36.15±6.21	43.22±9.22	21.96±11.01	57.66±6.29
12	83	46.09±6.43	8.74±5.08	37.35±6.48	42.91±8.70	20.25±10.38	58.99±6.21
13	102	48.65±6.27	10.43±4.95	38.22±5.23	43.51±8.24	23.58±10.90	60.87±6.24
14	100	48.69±5.62	10.31±4.22	38.38±5.27	43.94±7.76	22.19±9.89	60.14±5.46
15	100	49.41±5.50	10.15±4.61	39.27±4.90	44.51±7.10	23.27±9.95	61.03±5.28
16	100	49.46±5.72	10.22±4.39	39.23±4.97	44.70±7.44	22.00±9.87	60.33±5.72
17	100	49.78±5.98	9.99±4.60	39.78±4.84	44.37±7.53	22.38±11.03	61.17±6.23
Total	1018	46.77±6.38	9.51±5.06	37.26±5.77	42.98±8.06	21.27±9.96	58.71±6.17

Data are shown as mean±standard deviation. PI: pelvic incidence, PT: pelvic tilt, SS: sacral slope, LL: lumbar lordosis, SK: sacral kyphosis, SPI: sacrum pubic incidence

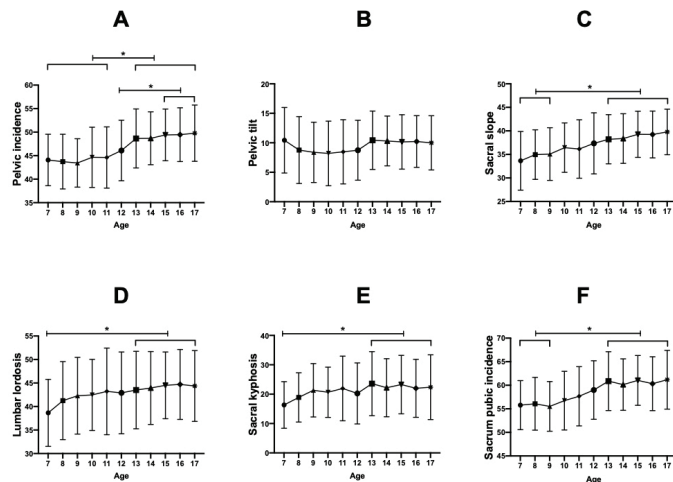


Figure 3. 3A. Age-related change of PI. PI values show a statistically significant difference between the 7-11 and 13-17 age groups and between the 12 and 15-17 age groups ($p < 0.01$) 3B. Age-related change of PT. PT values did not differ statistically between age groups ($p > 0.05$) 3C. Age-related change of SS. SS values show statistically significant differences between 7-9 and 13-17 age groups ($p < 0.01$) 3D. Age-related change of LL. LL values show statistically significant differences between 7 and 13-17 age groups ($p < 0.01$) 3E. Age-related change of SK. SK values show statistically significant differences between 7 and 13-17 age groups ($p < 0.01$) 3F. Age-related change of SPI. SPI values show statistically significant differences between 7-9 and 13-17 age groups ($p < 0.01$)

Method Comparison and Estimating of Pelvic Incidence

The SPI shows a very strong positive correlation with the PI (Figure 4). SPI cannot be used as a substitute for PI. However, this value is sensitive for the estimation of the PI value in cases where the PI cannot be measured. For PI estimation, the formula $SPI = 0.97(PI) + 13.38$ can be used (Table 3).

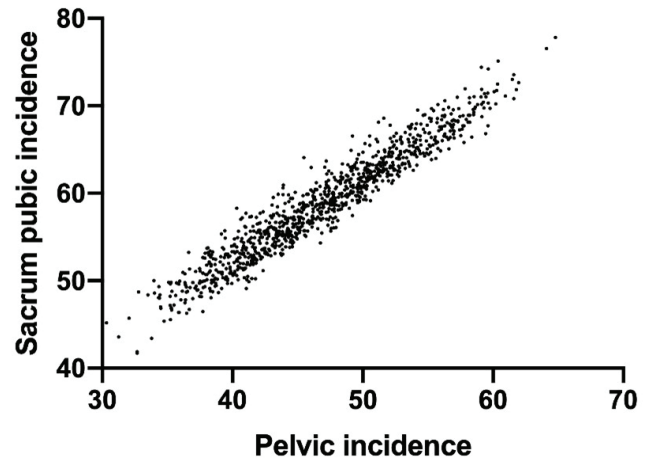


Figure 4. Correlations of PI and SPI. The clustering of points close to a linear line indicates a very strong positive correlation between PI and SPI

Table 3. Method comparison

Variable	Passing-Bablok		ICC	CCC	
	β_0 (95%)	β_1 (95%)	Coefficient	p value	
PI-SPI	13.38 (12.55-14.26)	0.97 (0.95-0.98)	0.96 (0.96-0.97)	<0.001	Coefficient 0.34 (0.32-0.36)

PI: pelvic incidence, SPI: sacrum public incidence, ICC: intraclass correlation coefficient, CCC: concordance correlation coefficient

DISCUSSION

In order to follow the progression of deformities in patients with spinal deformities and to plan appropriate treatment for these disorders, it is necessary to know the normal value ranges of spinopelvic parameters in individuals without spinal deformities. Many studies have shown that pelvic parameters are in a great relationship with the spinal sagittal balance, especially lumbar lordosis, and the importance of considering the spine and pelvis as a whole has been mentioned (8,10). There are few studies examining the spinopelvic parameters of healthy children and adolescents in the Turkish population. Our aim in this study is to determine the normal spinopelvic parameter ranges in healthy Turkish child and adolescent population and to use them as an aid in surgical planning in pediatric individuals with spinal deformity.

In studies in the literature, lateral radiography images, magnetic resonance images and three-dimensional CT images were used to calculate spinopelvic parameter values. On lateral radiographs, rotation of the pelvic skeleton may occur during acquisition, and therefore the two femoral heads do not always coincide. In such cases, the intersection of the two femoral heads is taken as a reference for measurement.

Iplikcioglu et al., showed that spinopelvic parameters measured using CT have high validity and reliability (19). Tyrakowski et al., Vrtovec et al. and Chen et al., reported that there is less margin of error in the measurement of pelvic parameters using three-dimensional CT compared to lateral radiography (20-22). Therefore, in our study, the measurement of pelvic parameters was made using a three-dimensional pelvic skeleton model.

In the literature, there are studies examining the change in pelvic incidence in healthy children and adolescents belonging to the Turkish population or other populations (Table 4). In the studies reviewed, Bailey et al. reported that pelvic incidence did not increase with age; other studies reported that pelvic incidence increases with age and a statistically significant difference was found between age groups (5,8,15,23-25). In addition, Mac-Thiong et al., Tonbul et al. and Abelin-Genevois et al. reported in their study that there was no statistically significant difference between the mean pelvic incidence values in male and female individuals (5,15,23,25). In our study, the mean pelvic incidence value in men and women was found to be 46.52 ± 6.0 and 47.03 ± 6.6 , respectively, while the mean pelvic incidence value of all individuals included in the study was found to be 46.77 ± 6.3 . In our study, it is seen

that the pelvic incidence increases with age, and there is no statistically significant difference between the mean pelvic incidence values in male and female individuals. Our results are compatible with the literature.

There are studies in the literature examining the pelvic tilt changes of healthy children and adolescents from the Turkish population or other populations (Table 4). In the studies reviewed, Abelin-Genevois et al. reported that pelvic tilt value did not increase with age in their study, while Mac-Thiong et al. and Tonbul et al. reported that

pelvic tilt value increases with age and a statistically significant difference was found between age groups (5,15,23). In our study, there was no increase in pelvic tilt value with age. We think that this may be due to the method used and the fact that our study includes a more limited age group compared to other studies. It has been reported that there is no statistically significant difference between the mean pelvic tilt values in men and women in all studies examined. The results of our study are also compatible with the literature.

Table 4. Comparison of studies in the literature

Studies	Age groups	UM and n	PI		PT		SS		LL	
			Mean±SD	M/F	Mean±SD	M/F	Mean±SD	M/F	Mean±SD	M/F
Hanson et al.	11-17	R- 40	47.4±7.5	-	-	-	-	-	58.2±11.5	-
	18-60		57.0±11.5	-	-	-	-	-	58.3±10.8	-
Mac-Thiong et al. (2004)	4-9	R- 180 (68 M, 112 F)	44.6±10.6	-	4.3±8.1	-	40.3±8.7	-	45.6±12.1	-
	10-18		49.3±11.2	-	7.9±7.7	-	41.4±8.5	-	49.2±12.4	-
Mac-Thiong et al. (2007)	3-18	R-341 (137 M, 204 F)	49.1±11.0	49.2±11.2 49.7±10.7	7.7±8.0	6.5±7.5 8.5±8.3	41.4±8.2	41.7±8.4 41.2±8.0	48.0±11.7	46.6±10.8 48.8±12.2
Tonbul et al.	3-18	R- 120 (60 M, 60 F)	49.0±10.0	49.4±11.4 49.6±10.8	7.8±8,1	6.7±7.8 8.7±8.4	42.4±8.6	42.8±8.7 42.2±8.3	-	-
Abelin-Genevois et al.	3-18	R- 85 (40 M, 45 F)	44.5±7.6	45.3 43.8	5.4±5.9	6.1 4.7	39.2±8.1	39.2 39.2	45.1±9.8	44.1 47.7
Bailey et al.	2-9	3CT-144 (118 M, 26 F)	44.0±6.5	-	-	-	-	-	34.2±6.9	-
	10-14		48.1±8.5	-	-	-	-	-	42.4±8.7	-
	15-20		46.6±8.4	-	-	-	-	-	43.1±8.0	-
Sevinc et al.	13-40	MR-413 (188 M, 225 F)	-	-	-	-	35.36±7.6	34.68±7.7 37.06±8.3	43.21±9.9	40.94±10.1 47.24±11.1
Tokpinar et al.	1-16	MR-321	-	-	-	-	-	-	28.0±7.3	-
Current study	7-17	3CT-1018 (515 M, 503 F)	46.77±6.3	46.52±6.0 47.03±6.6	9.51±5.06	9.54±4.91 9.49±5.21	37.26±5.7	36.98±5.6 37.54±5.9	42.98±8.0	42.01±7.5 43.97±8.4

UM: modality used, MR: magnetic resonance, 3CT: 3D computed tomography, R: radiography, M: male, F: female, n: number of samples, PI: pelvic incidence, PT: pelvic tilt, SS: sacral slope, LL: lumbar lordosis

In the literature, there are studies examining the change in the value of the sacral slope in healthy children and adolescents belonging to the Turkish population or other populations (Table 4). In the studies reviewed, Sevinç et al. and Abelin-Genevois et al. found a significant difference between the mean sacral slope values in men and women, Mac-Thiong et al. and Tonbul et al., on the other hand, reported that there was no significant difference between the mean sacral slope values in men and women in their studies (5,15,23,25,26). In our study, the mean sacral slope values in male and female individuals were calculated as 36.98±5.6 and 37.54±5.9, respectively, and no statistically significant difference was found between the two groups.

Studies have reported that the increase in sacral slope with age is not statistically significant. In our study, this

increase was statistically significant between the 7 and 12-17 age groups. We think that this difference may be due to the narrower age group included in the study compared to other studies, the use of different modalities, and the differences between populations.

In the studies examined, it is seen that the mean lumbar lordosis value differs between men and women. Mac-Thiong et al. did not find this difference statistically significant, while other studies found this difference between genders statistically significant (8,15,23,26,27). In our study, mean lumbar lordosis values in male and female individuals were found to be 42.01±7.5 and 43.97±8.4, respectively, and a statistically significant difference was observed between the two groups. The result of our study is compatible with the literature.

Hanson et al. found the lumbar lordosis value by measuring the T12-S1 interval in their study (24). Sevinç et al. found the lumbar lordosis value by measuring the L1-S1 interval in their study (26). Tokpinar et al., on the other hand, found the lumbar lordosis value by measuring the L1-L5 interval in their study (27). In our study, the lumbar lordosis value was found by measuring the L1-S1 interval. Measurement values at the same level were found at different intervals in different studies. This is due to differences in measurement methods. (Table 4).

McKay et al. reported the mean pelvic incidence and sacral kyphosis values as 55.3° and 35.1°, respectively, in their study on healthy adults (11). They reported a statistically significant relationship between pelvic incidence and sacral kyphosis ($r=0.636$, $p<0.001$). Baker et al. reported mean pelvic incidence and sacral kyphosis values as 50.1±10.08° and 24.2±13.1°, respectively, in their study on healthy adults (9). They reported a statistically significant correlation between pelvic incidence and sacral kyphosis ($r=0.796$, $p<0.05$). In our study, mean pelvic incidence and sacral kyphosis values were calculated as 46.77±6.38° and 21.27±9.96°, respectively. There is a significant relationship between pelvic incidence and sacral kyphosis ($r=0.606$, $p<0.01$). The result of our study showed that the relationship between these parameters in children and adolescents is similar to the relationship in adults. Due to an anatomical relationship between sacral kyphosis and sacral slope, we think that the increase in sacral kyphosis will affect the sacral slope and therefore the pelvic incidence will be affected. The positive correlation they found between pelvic incidence and sacral kyphosis supports this.

Wang et al. reported mean pelvic incidence and sacrum pubic incidence values as 46.9±9.9°, 68.3±9.4° in women, and 44.6±9.0° and 64.4±9.5° in men, in a study they conducted on healthy adults (7). They reported that there was no statistically significant difference between mean pelvic incidence and sacrum pubic incidence values in men and women ($p>0.05$). They reported a statistically significant relationship between pelvic incidence and sacrum pubic incidence ($r=0.958$, $p<0.01$, respectively). They reported that sacrum pubic incidence is a sensitive parameter that can be used in the estimation of pelvic incidence. In our study, mean pelvic incidence and sacrum pubic incidence values were calculated as 47.03±6.68°, 58.9±6.50° in women and 46.52±6.07° and 58.54±5.84° in men, respectively. It is seen that there is no statistically significant difference between mean pelvic incidence and sacrum pubic incidence values in men and women ($p>0.05$). There is a statistically significant relationship between pelvic incidence and sacrum pubic incidence ($r=0.962$, $p<0.001$). We can say that sacrum pubic incidence has a very strong relationship with the pelvic incidence, and this parameter can be used to estimate the pelvic incidence.

CONCLUSION

As a result, it is important to know the normal sagittal values of the spine, which performs many functions in a

healthy individual. Sacral slope, pelvic incidence, lumbar lordosis tend to increase with age during childhood and adolescence to maintain adequate sagittal balance during growth. Unlike other studies of the Turkish population, we used a larger sample size and evaluated more parameters to determine the normative values of spinopelvic parameters of the Turkish population. In addition, we performed our measurements on a three-dimensional model of the pelvis skeleton, which, unlike other studies, gave more precise results. We believe that this study, in which we examined the changes in spinopelvic parameters in healthy individuals during childhood and adolescence, will contribute to the literature and give clinicians ideas for sagittal corrections in spine and pelvis surgery.

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Conflict of interest: The authors have no conflicts of interest to declare.

Ethical approval: This study was carried out with the scope of the approval and information of Erciyes University Clinical Research Ethics Committee (Date and Decision No: 2019/587).

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REFERENCES

1. Le Huec JC, Aunoble S, Philippe L, Nicolas P. Pelvic parameters: origin and significance. *Eur Spine J.* 2011;20:564-71.
2. Roussouly P, Gollogly S, Berthonnaud E, Dimnet J. Classification of the normal variation in the sagittal alignment of the human lumbar spine and pelvis in the standing position. *Spine (Phila Pa 1976).* 2005;30:346-53.
3. Yucekul A, Ozpinar A, Kilickan FDB, et al. Relationship between pelvic incidence-adjusted relative spinopelvic parameters, global sagittal alignment and lower extremity compensations. *Eur Spine J.* 2023;32:3599-607.
4. Tan TH, Tan JH, Hey HWD. Changes in spinopelvic parameters between standing and sitting postures: a systematic review and meta-analysis. *Clin Spine Surg.* 2024;37:97-113.
5. Tonbul M, Güzelant AY, Gökçe A, et al. T Spinopelvic parameters in a turkish population: a study on 120 healthy individuals that could facilitate treatment planning. *Turkiye Klinikleri J Med Sci.* 2012;32:670.
6. Legaye J, Duval-Beaupere G, Hecquet J, Marty C. Pelvic incidence: a fundamental pelvic parameter for three-dimensional regulation of spinal sagittal curves. *Eur Spine J.* 1998;7:99-103.
7. Wang W, Wu M, Liu Z, et al. Sacrum pubic incidence and sacrum pubic posterior angle: two morphologic radiological parameters in assessing pelvic sagittal alignment in human adults. *Eur Spine J.* 2014;23:1427-32.
8. Bailey JF, Shefi S, Soudack M, et al. Development of pelvic incidence and lumbar lordosis in children and adolescents. *Anat Rec (Hoboken).* 2019;302:2132-9.

9. Baker JF, Don AS, Robertson PA. Pelvic incidence: computed tomography study evaluating correlation with sagittal sacropelvic parameters. *Clin Anat.* 2020;33:237-44.
10. Celestre PC, Dimar JR 2nd, Glassman SD. Spinopelvic parameters: lumbar lordosis, pelvic incidence, pelvic tilt, and sacral slope: what does a spine surgeon need to know to plan a lumbar deformity correction?. *Neurosurg Clin N Am.* 2018;29:323-9.
11. McKay G, Torrie PA, Dempster G, et al. The relationship between sacral kyphosis and pelvic incidence. *Asian Spine J.* 2018;12:74-9.
12. Karademir M, Karavelioglu E, Boyaci M, Eser O. The importance of the sagittal balance of the spine and spinopelvic parameters. *The Journal of Turkish Spinal Surgery.* 2014;25:139-48.
13. Arima H, Dimar JR 2nd, Glassman SD, et al. Differences in lumbar and pelvic parameters among African American, Caucasian and Asian populations. *Eur Spine J.* 2018;27:2990-8.
14. Lee CS, Chung SS, Kang KC, et al. Normal patterns of sagittal alignment of the spine in young adults radiological analysis in a Korean population. *Spine (Phila Pa 1976).* 2011;36:E1648-54.
15. Mac-Thiong J-M, Labelle H, Berthonnaud E, et al. Sagittal spinopelvic balance in normal children and adolescents. *Eur Spine J.* 2007;16:227-34.
16. Mac-Thiong J-M, Labelle H, Roussouly P. Pediatric sagittal alignment. *Eur Spine J.* 2011;20:586-90.
17. Zhou XY, Zhao J, Li B, et al. Assessment of sagittal spinopelvic balance in a population of normal Chinese children. *Spine (Phila Pa 1976).* 2020;45:E787-91.
18. Wang Z, Parent S, Mac-Thiong JM, et al. Influence of sacral morphology in developmental spondylolisthesis. *Spine (Phila Pa 1976).* 2008;33:2185-91.
19. İplikçioğlu AC, Karabağ H. Validity and reliability of spinopelvic parameters measured on computed tomography. *Int J Spine Surg.* 2022;16:875-80.
20. Chen HF, Mi J, Zhang HH, Zhao CQ. Pelvic incidence measurement using a computed tomography data-based three-dimensional pelvic model. *J Orthop Surg Res.* 2019;14:13.
21. Tyrakowski M, Wojtera-Tyrakowska D, Siemionow K. Influence of pelvic rotation on pelvic incidence, pelvic tilt, and sacral slope. *Spine (Phila Pa 1976).* 2014;39:E1276-83.
22. Vrtovec T, Janssen MM, Pernus F, et al. Analysis of pelvic incidence from 3-dimensional images of a normal population. *Spine (Phila Pa 1976).* 2012;37:E479-85.
23. Abelin-Genevois K, Idjerouidene A, Roussouly P, et al. Cervical spine alignment in the pediatric population: a radiographic normative study of 150 asymptomatic patients. *Eur Spine J.* 2014;23:1442-8.
24. Hanson DS, Bridwell KH, Rhee JM, Lenke LG. Correlation of pelvic incidence with low- and high-grade isthmic spondylolisthesis. *Spine (Phila Pa 1976).* 2002;27:2026-9.
25. Mac-Thiong JM, Berthonnaud E, Dimar JR 2nd, et al. Sagittal alignment of the spine and pelvis during growth. *Spine (Phila Pa 1976).* 2004;29:1642-7.
26. Sevinc O, Is M, Barut C, et al. Sagittal alignment of the lumbar spine in a Turkish population. *Neurosciences (Riyadh).* 2007;12:221-5.
27. Tokpinar A, Ulger H, Yilmaz S, et al. Examination of inclinations in spine at childhood and adolescence stage. *Folia Morphol (Warsz).* 2018;78:47-53.



Comparison of Conservative and Arthroplasty Treatment for 3 or 4 Part Proximal Humerus Fractures in the Elderly

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Abstract

Aim: Proximal humerus fractures are common injuries in the elderly population. This study hypothesizes that arthroplasty is not superior to conservative treatment in the management of multi-part proximal humerus fractures in elderly patients.

Material and Method: Patients aged 65 and above with 3–4-part proximal humerus fractures, treated either conservatively or with arthroplasty, were included in the study. The minimum follow-up period was set at 12 months. Functional evaluations of the patients were performed using the Quick Disabilities of Arm, Shoulder and Hand (Q-DASH) scoring system. Statistical analysis comparing the two groups was conducted using the SPSS software. The mean values of numerical data were analyzed using the Mann-Whitney U test, while categorical data were compared using the Chi-square test. A significant level of 0.05 was considered.

Results: A total of 67 patients who received adequate clinical follow-up were included in the study (50 conservative 17 arthroplasty). The average age of the patients was 76.12 years, with 9 male and 58 female patients. The average follow-up period was 22.61 months (range: 12-82). There were no statistically significant differences in age, gender, side, follow-up period, and fracture type distribution between the two groups. However, a significant difference in Q-DASH scores was observed ($p < 0.05$).

Conclusion: In the treatment of proximal humerus fractures, even when they are multi-part fractures, conservative treatment should be the first choice. We think that the early results of conservative treatment are better than arthroplasty.

Keywords: Proximal humerus fracture, conservative treatment, shoulder arthroplasty

INTRODUCTION

Proximal humerus fractures represent a frequent occurrence among the elderly and pose considerable dilemmas in determining the most appropriate course of treatment (1,2). Given the functional impairment and diminished quality of life associated with these fractures, especially those categorized as 3- or 4-part fractures, selecting the optimal treatment approach remains a subject of ongoing discussion among orthopedic specialists (1,2).

Traditionally, conservative management, including sling immobilization, early motion exercises, and physical therapy, has been the preferred approach for managing proximal humerus fractures in the elderly (1). This conservative approach aims to achieve fracture healing, pain relief, and restoration of shoulder function without the

need for surgical intervention. However, recent advances in surgical techniques and implant designs have led to the increased utilization of arthroplasty as an alternative treatment modality (2,3).

Arthroplasty, encompassing both hemiarthroplasty and reverse shoulder arthroplasty (RSA), offers the potential benefits of immediate stability, anatomical alignment, and improved functional outcomes (3). This surgical intervention replaces the damaged or fractured proximal humerus with an artificial joint, thus providing structural support and facilitating early rehabilitation (4). Despite the growing popularity of arthroplasty, the optimal treatment strategy for elderly patients with 3- or 4-part proximal humerus fractures remains a subject of ongoing investigation.

By comparing the outcomes of conservative management

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and arthroplasty, we seek to shed light on the relative efficacy, functional outcomes, and complications associated with each approach. The aim of our study is to contribute to the ongoing discussion surrounding the treatment of 3- or 4-part proximal humerus fractures in the elderly population (5).

MATERIAL AND METHOD

After obtaining ethical approval from the institutional review board, patients with proximal humerus fractures who were treated conservatively or with arthroplasty between 2011 and 2019 at our clinic were included in the study. Three or four-part displaced fractures were identified using direct radiographs and computed tomography images (according to Neer classification, types III and IV) (2). Patients aged 65 and above at the time of fracture occurrence were enrolled in the study. Patients under 65 years old, those with pathological fractures, those who could not be clinically followed, non-displaced or two-part fractures, those treated with plates, screws, or K-wires, patients with inadequate clinical follow-up or significant cognitive impairment, and those with advanced systemic conditions were excluded from the study. Patients who underwent surgery within 1 month after the fracture occurred were included in this study. Arthroplasty patients who underwent later sequelae after bone union were not included in the study. Reverse shoulder arthroplasty was preferred for patients with no additional health problems and better bone quality, and hemiarthroplasty was preferred for patients who were older and had lower expectations.

In the conservative treatment group, patients were followed with a shoulder-arm sling for three weeks. All patients in this group had declined surgical intervention despite being recommended due to fracture displacement. Reduction with simple traction was attempted in fracture-dislocation patients. In case of non-reduction, surgical treatment was recommended to the patients, but patients who did not accept were followed in the conservative group. Fracture union evaluation was performed using direct radiographs after the follow-up period. Elbow and wrist movements were initiated by removing the shoulder-arm sling. Shoulder movements were initiated after removing the sling (Figure 1).

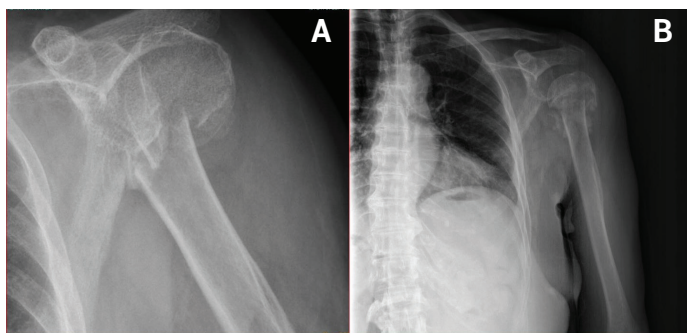


Figure 1. A. Four-part proximal humerus fracture, at the time of presentation B. At the end of the conservative treatment of the same patient

Surgical procedures of patients who underwent arthroplasty were performed by the authors who contributed to the article. Patients who underwent arthroplasty were operated on under general anesthesia in the beach chair position. The procedure was performed through a deltopectoral incision. Tubercle fragments were secured with 5-0 Ethicon sutures. The humeral head was excised, and the humerus was reamed. Although cement was used only in some reverse shoulder prostheses, it was not used in hemiarthroplasty patients. For patients who received reverse shoulder prostheses, glenoid reaming was performed. The glenoid component was placed and fixed with 3-4 locking screws. A glenosphere was inserted, a reverse polyethylene cup was placed on the humeral component, and joint reduction was performed. Once stability was achieved, tubercles were anatomically reduced and fixed in place using sutures passed through the prosthesis or the humerus. Prophylactic antibiotics were administered for 48 hours postoperatively. Deep vein thrombosis prophylaxis was initiated with subcutaneous enoxaparin sodium 0.4 cc for 10 days. Patients were followed with a shoulder-arm sling for two weeks. Elbow and hand movements were initiated immediately after surgery. Pendulum exercises were initiated, followed by gentle passive movements based on the patient's tolerance. Depending on the patient's condition, active movements were introduced from the second week to the first month, and patients were followed with the assistance of the physiotherapy unit (Figure 2).

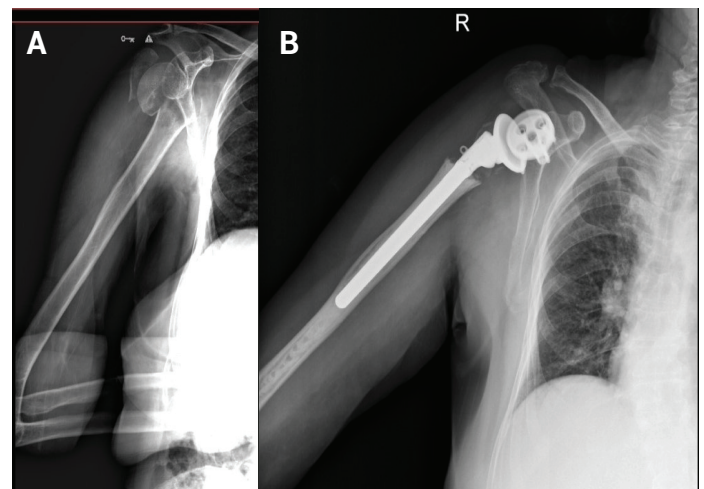


Figure 2. A. Four-part proximal humerus fracture, preoperative x-ray B. Post operative x-ray of the patient. The treatment was reverse shoulder arthroplasty

The clinical evaluation of patients was performed using the Quick Disabilities of Arm Shoulder and Hand (Q-DASH) scoring system. Q-DASH scoring was routinely applied after the first year after surgery. Some of the patients had their scores evaluated at outpatient clinic controls, and some of them were called by phone. The application of the scores was done by the physiotherapists working in our clinic, both in the outpatient clinic and by phone call.

Statistical analysis involved using mean and median values for numerical data and rates/percentages for

categorical data. The Shapiro-Wilk test was used to assess the normality of the numerical data distribution. Parametric tests were employed to compare two groups when the data followed a normal distribution, and nonparametric tests were used when the data did not follow a normal distribution. The chi-square test was used for the evaluation of categorical data. Fisher's exact test was used when the observed table value was less than 5. A significance level of $p < 0.05$ was considered statistically significant.

RESULTS

A total of 131 patients were treated for proximal humerus fractures classified as three or four-part fractures. Among them, 27 patients were treated with plates and screws. Due to differences in the age distribution of patients treated with plates and screws, they were excluded from the study. The remaining 104 patients were treated with either conservative or arthroplasty methods. Out of the 104 patients, 67 patients were included in the study after excluding those who could not be clinically followed, had several reasons for mortality, or lacked sufficient cognitive ability for functional scoring. Among these patients, 50 were treated conservatively, and 17 underwent arthroplasty (Table 1). Among the patients who underwent

arthroplasty, four received hemiarthroplasty, and 13 received reverse shoulder prosthesis.

The average age of the patients was 76.12 (range: 65-87) years. There were nine male patients (13.4%) and 58 female patients (86.6%). Treatment was performed on the right side in 42 patients (62.7%) and on the left side in 25 patients (37.3%). The average follow-up period was 22.61 months (range: 12-82). Fracture-dislocations were observed in 14 patients, three-part fractures in 22 patients, and four-part fractures in 31 patients. The statistical analysis showed no significant differences between the two groups in terms of age, gender, side, follow-up period, and fracture type distribution ($p > 0.05$) (Table 1). The average Q-DASH scores of the patients were 21.68 (range: 0-70.45). The average Q-DASH score was 15.59 for patients treated conservatively, while it was 39.57 for those who underwent arthroplasty. There was a statistically significant difference between the two groups ($p < 0.05$, Mann Whitney U test) (Table 1).

There were two complications after arthroplasty; one periprosthetic fracture and the other was a dislocation. There was no infection in our series. We did not have any patients in the conservatively treated group with nonunion, infection, or additional instability.

Table 1. Statistical comparison of general demographic values and clinical score (Quick Disabilities of Arm, Shoulder, and Hand; Q-DASH)

		Conservative		Arthroplasty		All	p value	
Number of patients		50	75%	17	25%	67	-	
Mean age (years)		76.12	+/- 6.79	76.12	+/- 4.76	76.12	0.954	
Gender	Male	6	12.0%	3	17.6%	9	13.4%	0.682
	Female	44	88.0%	14	82.4%	58	86.6%	
Side	Right	32	64.0%	10	41.2%	42	62.7%	0.703
	Left	18	36.0%	7	58.8%	25	37.3%	
Mean follow-up time (months)		23.74	+/- 17.17	19.29	+/- 4.31	22.61	0.608	
Fracture type	Fractured dislocation	8	16.0%	6	35.3%	14	20.9%	0.157
	Three parts	16	32.0%	6	35.3%	22	32.8%	
	Four parts	26	52.0%	5	29.4%	31	46.3%	
Mean Q-DASH score		15.59	+/- 11.95	39.57	+/- 15.20		<0.001	

DISCUSSION

The optimal treatment strategy for elderly patients with 3- or 4-part proximal humerus fractures remains a subject of ongoing investigation. Proximal humerus fractures in the elderly population can have a substantial impact on functional capacity and quality of life. Traditionally, conservative management has been the preferred approach, aiming to achieve fracture healing, pain relief, and restoration of shoulder function without surgical intervention (1). The main finding of this study shows that there is a statistically significant difference between conservative treatment and arthroplasty treatment. The Q-DASH scores of the patients who underwent conservative treatment were found to be lower than the patients who underwent arthroplasty. This result shows that conservative treatment provides better clinical

outcomes.

However, recent advances in surgical techniques and implant designs have led to the increased utilization of arthroplasty as an alternative treatment modality (6). Arthroplasty offers potential benefits such as immediate stability, anatomical alignment, and improved functional outcomes (3,6). Studies have shown that arthroplasty can provide structural support and facilitate early rehabilitation by replacing the damaged or fractured proximal humerus with an artificial joint (4). Due to the elevated risk of osteoporosis, bone defects, graft requirements, and osteonecrosis, arthroplasty is preferred over internal fixation (7). In these studies, the risk of osteonecrosis in proximal humerus fractures in elderly and osteoporotic patients has been reported to be between 16% and 22% (8-10). Additionally, poor outcomes have been reported

due to tuberosity displacement and improper positioning of the humeral head (2,7,11). However, some studies have shown that a significant portion of patients with radiological avascular necrosis are minimally symptomatic or asymptomatic (2,11). In elderly patients with poor expectations, tuberosity displacement or varus-valgus angulation may have fewer clinical implications (2,11). Some authors have recommended arthroplasty for 3- or 4-part proximal humerus fractures in the elderly (12). While hemiarthroplasty was preferred in previous years, reverse shoulder arthroplasty is currently more favored (13). In our study, the arthroplasty group, we observed unfavorable outcomes.

Nevertheless, in recent years, there has been an increase in publications reporting that conservative treatment yields fewer complications and better clinical outcomes, particularly in elderly patients with poor bone quality, low expectations, and additional comorbidities (2,11). Postoperative complications such as instability (2-31%), infection (1-15%), scapular notching (44-96%), glenoid loosening (5-38%), tubercular malposition (50%) and anesthesia-related complications are frequently observed after arthroplasty (2,14). However, these issues are not seen in patients undergoing conservative management. Avascular necrosis, malunion, and nonunion, which may occur in conservatively managed patients, are not as common in this age group. Therefore, recent publications have begun reporting better outcomes in conservatively treated proximal humerus fractures, especially in elderly patients (15-18). Our patient group also achieved statistically better clinical outcomes in the conservative group ($p < 0.05$).

Our study aimed to compare the outcomes of conservative management and arthroplasty treatment for elderly patients with 3- or 4-part proximal humerus fractures. It is crucial to consider patient-specific factors when selecting the optimal treatment approach. Age, fracture displacement, bone quality, comorbidities, and patient expectations should all be considered (19,20). By evaluating these factors and their impact on treatment outcomes, our study provides a comprehensive assessment of the benefits and risks associated with conservative and arthroplasty treatment options for elderly patients with 3- or 4-part proximal humerus fractures. In our analysis, we found no significant differences in age, gender, side, follow-up period, and fracture type distribution between the conservative management and arthroplasty groups ($p > 0.05$). However, there was a statistically significant difference in the average Q-DASH scores between the two groups ($p < 0.05$, Mann Whitney U test). The conservative treatment group had lower Q-DASH scores (15.59) compared to the arthroplasty group (39.57), indicating better functional outcomes in the conservative management group (3,15,16).

While arthroplasty may offer immediate stability and anatomical alignment, it is important to consider the potential complications associated with surgery, such as infection, implant failure, and limited implant longevity (4). On the other hand, conservative management aims to

avoid surgical intervention and its associated risks. Our findings support the notion that conservative management can achieve satisfactory functional outcomes for elderly patients with 3- or 4-part proximal humerus fractures (1,15-18).

This study has limitations. Retrospective studies rely on existing medical records, and there may be variations in the documentation and availability of information, potentially impacting the accuracy and completeness of the data analyzed. The sample size was relatively small. The decision to choose between conservative and arthroplasty treatments was not randomized but based on individual patient factors and preferences. Among the patients who underwent arthroplasty, some patients had hemiarthroplasty, and some had reverse shoulder arthroplasty. Further research with larger sample sizes and multi-center studies would be beneficial to validate our findings and provide more robust evidence for treatment decision-making in this patient population. Q-DASH scoring is subjective rather than objective scoring. It is a patient dependent score. It does not look at data such as joint range of motion and muscle strength. This issue should be taken into consideration when evaluating Q-DASH scoring. Our follow-up period was not sufficient for the development of posttraumatic arthrosis in the conservatively treated group.

CONCLUSION

In conclusion, our study adds to the ongoing discussion surrounding the treatment of 3- or 4-part proximal humerus fractures in elderly patients. Based on our findings, conservative management can offer satisfactory functional outcomes for elderly patients, while arthroplasty may be considered in select cases where immediate stability and anatomical alignment are crucial. Clinical judgment and patient preferences should guide treatment decisions, considering individual patient factors. Future research should aim to further clarify the optimal treatment strategy by addressing the limitations of our study and conducting larger-scale investigations.

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REFERENCES

1. Handoll HH, Ollivere BJ. Interventions for treating proximal humeral fractures in adults. *Cochrane Database Syst Rev.* 2010;12:CD000434.
2. Kancherla VK, Singh A, Anakwenze OA. Management of acute proximal humeral fractures. *J Am Acad Orthop Surg.* 2017;25:42-52.

3. Rangan A, Handoll H, Brealey S, et al.; PROFHER trial collaborators. Surgical vs nonsurgical treatment of adults with displaced fractures of the proximal humerus: the PROFHER randomized clinical trial. *JAMA*. 2015;313:1037-47.
4. Tamimi I, Montesa G, Collado F, et al. Displaced proximal humeral fractures: when is surgery necessary?. *Injury*. 2015;46:1921-9.
5. O'Donnell JA, Gage MJ. Proximal humerus geriatric fracture care: fix, replace, or nonoperative treatment?. *J Orthop Trauma*. 2021;35:S6-10.
6. Gigis I, Nenopoulos A, Giannikas D, et al. Reverse shoulder arthroplasty for the treatment of 3 and 4- part fractures of the humeral head in the elderly. *Open Orthop J*. 2017;11:108-18.
7. Tepass A, Blumenstock G, Weise K, et al. Current strategies for the treatment of proximal humeral fractures: an analysis of a survey carried out at 348 hospitals in Germany, Austria, and Switzerland. *J Shoulder Elbow Surg*. 2013;22:e8-14.
8. Resch H, Povacz P, Fröhlich R, Wambacher M. Percutaneous fixation of three- and four-part fractures of the proximal humerus. *J Bone Joint Surg Br*. 1997;79:295-300.
9. Krappinger D, Bizzotto N, Riedmann S, et al. Predicting failure after surgical fixation of proximal humerus fractures. *Injury*. 2011;42:1283-8.
10. Large TM, Adams MR, Loeffler BJ, Gardner MJ. Posttraumatic avascular necrosis after proximal femur, proximal humerus, talar neck, and scaphoid fractures. *J Am Acad Orthop Surg*. 2019;27:794-805.
11. Jawa A, Burnikel D. Treatment of proximal humeral fractures: a critical analysis review. *JBJS Rev*. 2016;4:e2.
12. Antonios T, Bakti N, Phadkhe A, et al. Outcomes following arthroplasty for proximal humeral fractures. *J Clin Orthop Trauma*. 2020;11:S31-6.
13. Schairer WW, Nwachukwu BU, Lyman S, et al. Reverse shoulder arthroplasty versus hemiarthroplasty for treatment of proximal humerus fractures. *J Shoulder Elbow Surg*. 2015;24:1560-6.
14. Cheung E, Willis M, Walker M, et al. Complications in reverse total shoulder arthroplasty. *J Am Acad Orthop Surg*. 2011;19:439-49.
15. Roberson TA, Granade CM, Hunt Q, et al. Nonoperative management versus reverse shoulder arthroplasty for treatment of 3- and 4-part proximal humeral fractures in older adults. *J Shoulder Elbow Surg*. 2017;26:1017-22.
16. Erpala F, Tahta M, Öztürk T, Zengin Ç. Comparison of treatment options of three- and four-part humerus proximal fractures in patients over 50 years of age. *Cureus*. 2021;13:e17516.
17. Xie L, Ding F, Zhao Z, et al. Operative versus non-operative treatment in complex proximal humeral fractures: a meta-analysis of randomized controlled trials. *Springerplus*. 2015;4:728.
18. Song JQ, Deng XF, Wang YM, et al. Operative vs. nonoperative treatment for comminuted proximal humeral fractures in elderly patients: a current meta-analysis. *Acta Orthop Traumatol Turc*. 2015;49:345-53.
19. Osterhoff G, Ossendorf C, Wanner GA, et al. The calcar screw in angular stable plate fixation of proximal humeral fractures - a case study. *J Orthop Surg Res*. 2011;6:50.
20. Lopiz Y, Alcobia-Díaz B, Galán-Olleros M, et al. Reverse shoulder arthroplasty versus nonoperative treatment for 3- or 4-part proximal humeral fractures in elderly patients: a prospective randomized controlled trial. *J Shoulder Elbow Surg*. 2019;28:2259-71.



The Relationship of University Students' Internet Addiction Level Through Telephone Use and 2d:4d Ratio

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Abstract

Aim: To evaluate the relationship between the 2nd and 4th finger measurement ratio (2d:4d) ratio of university students' internet addiction level through phone use.

Material and Method: 322 students were questioned about their demographic data, dominant extremity, and the device while using the internet. Hand width (HW), length (HL), grip strength (HGS), 2d:4d measurements were taken. Young Internet Addiction Scale (YIAS) was used for internet addiction, Smartphone Addiction Scale-Short Form (SAS) was used for smartphone addiction.

Results: In men, it was determined that there was a statistically significant difference between the groups in terms of Right-Left HL, Left HGS, Right/4d, YIAS and SAS values. In addition, it was determined that the device preference, HL right, HL left, HGS left and Right/4d parameters originated from normal and dependent groups. It was determined that there was a statistically significant difference between the groups in women in terms of Left HL, Right/2d, Right/4d, Left/2d, Left/4d, Young and SAS values. It was determined that the device preference was due to individuals falling into the normal group of Left HL according to the YIAS, and the statistical difference of the Right/2d, Right/4d, Left/2d and Left/4d parameters. It was determined that there was a moderately strong negative correlation between SAS and Right/2d, Right/4d, Left/2d, Left/4d parameters in addicted men.

Conclusion: The gender relations of the accepted scales regarding phone and internet addiction may be due to the length of the left hand and the movement function of the right 4d to provide control in phone use, rather than the 2d:4d finger ratios.

Keywords: 2nd and 4th finger measurement ratio, internet, smartphone, addiction, university students

INTRODUCTION

Mobile phones, which entered our lives in the 90s with functions such as calling and message, have become important with the development of technology due to their many features such as internet use, video, photo taking, navigation and document transfer (1). While this developing technology makes life easier, it has also brought about internet addiction, which we can call the new concept of addiction (2). In the literature, Young defined internet addiction as the desire to use the internet excessively, the urge to constantly stay online, and extreme irritability and aggression due to deprivation (3). It is reported that university students, who are the group that uses the internet most intensively, have a high risk of internet addiction (4).

Nowadays, it is seen that unidirectional perspectives have begun to be replaced by multidisciplinary perspectives in

the evaluation of conditions affecting mental health such as attention deficit and hyperactivity disorder, autism spectrum disorder, substance use, addiction, anorexia nervosa, schizophrenia, depression, borderline personality disorder, antisocial personality disorder (Fusar-Poli et al., 2021). One of these approaches is the neurodevelopmental approach. The basis of neurodevelopmental diseases is related to development. In this context, developmental psychopathology may result from the interaction of both prenatal and postnatal periods (5). The ratio of the lengths of the second finger and fourth finger on the hand, known as 2d:4d is formed at the end of the first trimester in the prenatal period. This ratio is considered an indicator of testosterone and estrogen exposure. There is increasing data showing that high testosterone exposure is associated with behavioral problems, alcohol and substance use disorders, addictions and physical aggression (6).

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Additionally, at the systemic neuroscientific level, dysfunctions in the frontostriatal-limbic cycle have been observed in people suffering from internet addiction (7). While less is known at the molecular level underlying these neural dysfunctions, this study aimed to evaluate the relationship between university students' level of internet addiction through phone use and the 2d:4d ratio.

MATERIAL AND METHOD

This study is a cross-sectional analytical study. A total of 322 volunteer students, 126 male and 196 female, from Bandırma University Nursing and Physical Therapy and Rehabilitation Department students participated in the study. Criteria for inclusion in the study; being a university student, volunteering to participate in the study, and using a smartphone. Participants with hand and wrist diseases or a history of trauma were excluded from the study when measuring hands. This work was implemented with the approval of the Bandırma University Non-Interventional Clinical Ethics Committee (2022-165). The study complies with the ethical standards of the Declaration of Helsinki as revised in 2013.

Descriptive statistics median (min-max) values for the ages of male and female students: male-normal 19 (17-41), male-risky 19 (17-28), male-addicted 21 (17-28), female-normal 19 (17-33), female-risky 19 (17-39), female-addicted 20 (17-28) (Table 1).

A structured survey was administered to the participants regarding sociodemographic characteristics, telephone and internet usage. In the evaluation form (age, gender, height, weight, body mass index (BMI), dominant extremity, device used while using the internet) were recorded by the practitioner. In addition, hand width, hand length, hand grip strength, and 2d:4d measurements of the fingers were taken. Young Internet Addiction Scale was used for internet addiction, and Smartphone Addiction Scale-Short Form was used for smartphone addiction.

Evaluation Parameters

Hand Width (HW): The distance between the second and fifth metacarpophalangeal joints was measured with an electronic digital caliper (150 mm, 0.01 mm/0.0005 inch precision, Shan brand) (8) (Figure 1).

Hand Length (HL): The distance between the distal part of the styloid process of the radius and the tip of the longest finger was measured with a non-flexible tape measure (8) (Figure 1).

Hand Grip Strength (HGS): While the individual stood with his arms at his side and stood ready with a Saehan brand hand dynamometer in his hand, the measurement part of the dynamometer was held facing outwards. The dynamometer was tightened with maximal force. The test was applied twice for both hands and the best result was recorded in kilograms (8).

2nd and 4th finger measurement ratio (2d:4d): The length of the second finger and the fourth finger was measured twice with an electronic digital caliper (150 mm, Shan

brand with 0.01 mm/0.0005 inch precision) and written in cm (8) (Figure 1).

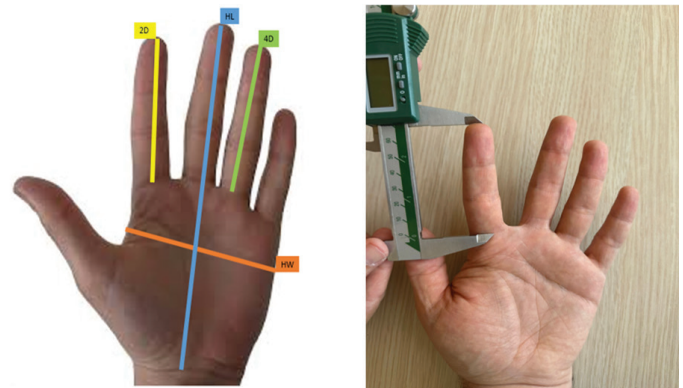


Figure 1. Hand width (HW), Hand length (HL), 2D (2th finger measurement), 4D (4th finger measurement)

Young Internet Addiction Scale (YIAS)

It is a 20-question self-assessment scale developed by Dr. Young and whose validity and reliability in Turkish has been proven by Balta et al. In studies on internet addiction, participants are asked to mark one of the "Never - 0 points", "Rarely - 1 point", "Sometimes - 2 points", "Often - 3 points", "Often - 4 points" or "Always - 5 points" options in response to the questions asked. From the survey, a total score of "80 and above" is defined as an internet addict, "between 50-79 points" is defined as a risky internet addict, and "49 points and below" is defined as an "average internet user" (9).

Smartphone Addiction Scale-Short Form (SAS)

The scale assessing smartphone addiction consists of 10 items with a 6-point Likert scale (1: I strongly disagree, 6: I strongly agree). While scores from the scale can be between 10 and 60, an increase in score indicates an increase in smartphone addiction (10).

Statistical Analysis

The suitability of the data for normal distribution was checked with the Kolmogorov Smirnov test and it was determined that the data did not show a normal distribution. Median, minimum (min) and maximum (max) values of data that did not show normal distribution were given. Kruskal Wallis H test was applied to compare men and women according to addiction groups. According to the results of the Kruskal Wallis H test, Mann Whitney U test was applied to the data as a Post Hoc test to find out which group caused the statistically significant difference. IBM SPSS Statistics 22.0 package program was used in the analyses. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 322 volunteers, 126 men and 196 women, participated in our study. According to the Young scale, addiction levels of individuals were divided into 3 groups: normal, risky and addicted individuals. Among men, it was determined that there were 46 participants considered normal, 35 participants considered risky, and 45 participants considered addicted according to their scale scores. Among women, it was determined that there

were 126 participants considered normal, 28 participants considered risky, and 41 participants considered addicted according to their scale scores. Median (min-max) values of the results showing age, height, weight and Body Mass Index (BMI), dominant extremity, and the technological device they use most in daily life according to the addiction

levels of men and women are given in Table 1. According to the analysis results of the Kruskal Wallis H Test between the groups, it was determined that there was no statistically significant difference in terms of demographic data, dominant extremity, and device preference according to the addiction levels of men and women ($p>0.05$), (Table 1).

Table 1. Demographic data, dominant extremity and device preference results of male and female participants

Gender	Group	Age	Height	Weight	BMI	Dominant ekstremity		Device preference			
						R	L	Phone	Tablet	Computer	All
Male	Normal	19 (17-41)	175 (157-189)	65 (50-88)	21.6 (17.3-27.7)	42	3	39	2	4	0
	Risky	19 (17-28)	174 (156-190)	69 (42-93)	22.4 (15.7-28.7)	32	4	27	2	3	4
	Addicted	21 (17-28)	173 (160-190)	70 (50-92)	23.1 (17.9-31.8)	39	6	28	4	2	11
	p value	.051	.148	.257	.056	.575		.014			
Female	Normal	19 (17-33)	163 (150-180)	57 (35-90)	20.8 (14.5-34.7)	121	5	123	2	1	0
	Risky	19 (17-39)	165 (150-172)	58 (45-94)	21.4 (18-34.5)	24	4	21	3	4	0
	Addicted	20 (17-28)	162 (150-179)	55 (45-89)	21.4 (16.5-29.7)	36	5	28	3	0	10
	p value	.052	.628	.766	.416	.061		<0.001			

R: right, L: left

Median (min-max) values of measurements taken from the right and left hands of men and women according to their addiction levels and 2D:4D ratios are given in Table 2. According to the results of the Kruskal Wallis H Test analysis, it was determined that there was a statistically significant difference between the groups in terms of right

hand length, left hand length, HGS left, Right/4d, Young and SAS values in men ($p<0.05$). According to the Kruskal Wallis H Test analysis results, it was determined that there was a statistically significant difference between the groups in terms of hand length left, Right/2d, Right/4d, Left/2d, Left/4d, Young and SAS values in women ($p<0.05$) (Table 2).

Table 2. Measurement values taken from the hands of men and women

	Parameters	Normal addicted	Risky addicted	Addicted	p value
Male	R-Hand width	86 (76.3-94.3)	87.7 (76.3-94.9)	86.4 (73.2-94.1)	.259
	L-Hand width	84.7 (74.3-95.6)	85.7 (75.8-99.1)	84 (71-93.3)	.226
	R-Hand length	189.7 (161.5-206.7)	192.6 (178.8-214)	187.4 (107.8-214)	.040
	L- Hand length	188 (160-207)	192 (173-215)	185.5 (107.8-215)	.048
	R-HGS	30.8 (18-41)	45.2 (25-78)	40 (15-78)	.111
	L-HGS	31.15 (18-43)	43.6 (17-62)	38 (17-62)	.039
	R/2d	71.8 (62.5-80.7)	73.7 (61.6-82.8)	74.5 (61.6-106.2)	.159
	R/4d	72.6 (60.3-84.7)	74.7 (63.8-85.2)	75.3 (62-95.1)	.025
	R (2d:4d)	.988 (.93-1.14)	.981 (.86-.1.08)	.985 (.91-1.12)	.822
	L/2d	71.4 (62.5-82)	73.1 (63.8-82.1)	73.1 (62-98.4)	.319
	L/4d	72.6 (60.8-84.4)	74.9 (65-85.1)	75.4 (60.4-94.4)	.216
	L (2d:4d)	.981 (.92-1.07)	.974 (.92-.1.1)	.980 (.91-1.10)	.539
	Young	37 (10-47)	53 (50-65)	81 (80-88)	.000
	SAS	30 (13-51)	38.5 (18-58)	45 (26-60)	.000
Female	R-Hand width	76.6 (64.6-89.7)	76.8 (67.5-90)	77.2 (67.5-92.4)	.439
	L-Hand width	74.9 (65.6-85.2)	75.4 (68.1-86.9)	75.5 (68.1-90.7)	.962
	R-Hand length	175.5 (148-196)	176.1 (159.9-193.1)	173 (140.1-199.1)	.209
	L- Hand length	175 (149.6-202)	177.1 (159.6-195)	170 (138.5-194)	.008
	R-HGS	23.9 (7-38)	24.9 (9-37)	24.5 (9-46)	.694
	L-HGS	21.8 (9-36)	24.3 (11-34)	23 (11-49)	.242
	R/2d	68 (57.7- 82.8)	68.5 (61.6-77)	70 (60-89.8)	.027
	R/4d	67.8 (59-83.8)	67.6 (60.9-78)	69.2 (60.1-89.8)	.034
	R (2d:4d)	.999 (.86-1.12)	1.00 (.94-.1.12)	1.01 (.94-1.10)	.450
	L/2d	67 (58.2-86.7)	67.3 (60.9-76.8)	70.2 (59.3-89.3)	.003
	L/4d	67 (58.4-84.9)	67.8 (61.8-78.1)	70.3 (58-84.6)	.003
	L (2d:4d)	.993 (.93-1.14)	.996 (.93-1.04)	1.00 (.92-1.10)	.394
	Young	28 (6-49)	52.5 (50-74)	81 (80-84)	.000
	SAS	26 (10-45)	37.5 (18-50)	45 (30-55)	.000

R: right, L: left, HGS: hand grip strength, SAS: Smartphone Addiction Scale

According to the analysis results, the device preference was determined by the normal-dependent groups of hand length right, hand length left, HGS left and Right/4d parameters. As a result of the analysis, it could not be concluded which group caused the difference for Young and SAS parameters in all pairwise comparisons (Table 3). In order to determine

which addiction group caused the difference in the men's device preference and the measurements taken from their hands, Mann Whitney U test was applied to the data as a Post Hoc test and a Pairwise Comparison table was created. Model viewer image of the analysis result is given in Table 4.

Table 3. Pairwise comparison results of parameters that differ between groups in men

Male	Device preference	R-Hand length	L-Hand length	L-HGS	R/4d	Young	SAS
Normal-risky	.568	.999	.999	.999	.127	.000	.005
Normal-addicted	.011	.049	.047	.037	.032	.000	.000
Risky-addicted	.457	.108	.126	.233	1.000	.000	.005

R: right, L: left, HGS: hand grip strength, SAS: Smartphone Addiction Scale

In order to determine which addiction group caused the difference in the women's device preference and the measurements taken from their hands, Mann Whitney U test was applied to the data as a Post Hoc test and a Pairwise Comparison table was created. According to the results of the analysis, it was determined that the device preference and hand length left were from

individuals in the normal group according to the Young scale, and the statistical difference in the parameters Right/2d, Right/4d, Left/2d, Left/4d was from the Normal-dependent groups. As a result of the analysis, it could not be concluded which group caused the difference for Young and SAS parameters in all pairwise comparisons (Table 4).

Table 4. Pairwise comparison results of parameters that differ between groups in women

Female	Device preference	L-hand length	R/2d	R/4d	L/2d	L/4d	Young	SAS
Normal-risky	.008	.010	1.000	1.000	1.000	.727	.000	.000
Normal-addicted	.000	.033	.021	.029	.002	.003	.000	.000
Risky-addicted	1.000	1.000	.466	.281	.222	.439	.038	.014

R: right, L: left, SAS: Smartphone Addiction Scale

Spearman Rho correlation analysis was applied to the data to determine how SAS, hand measurements and 2d:4d ratios changed. According to the analysis results, it was determined

that there was a moderately strong negative correlation between SAS and the parameters Right/2d, Right/4d, Left/2d, Left/4d in the group of men identified as addicts (Table 5).

Table 5. Spearman Rho correlation analysis results

Parameter	Test statistics	Male			Female		
		Normal	Risky	Addicted	Normal	Risky	Addicted
R-Hand width	r	-.164	.062	-.238	.056	-.082	.188
	p	.276	.722	.115	.533	.678	.239
L-Hand width	r	-.211	.043	-.147	-.029	-.070	.132
	p	.158	.807	.335	.744	.725	.410
R-Hand length	r	-.062	-.225	.155	.046	.263	.066
	p	.682	.195	.309	.605	.177	.683
L-Hand length	r	-.088	-.239	.173	.028	.246	.285
	p	.559	.168	.257	.756	.208	.070
R-HGS	r	.056	-0.30	-.289	.015	.270	-.125
	p	.713	.862	.054	.866	.164	.435
L-HGS	r	.129	-0.46	-.177	-.038	.189	-.021
	p	.392	.792	.244	.671	.336	.898
R/2d	r	-.088	-.214	-.421	.074	.123	-.171
	p	.559	.217	.004	.409	.532	.285
R/4d	r	.031	-0.90	-.378	.005	.168	-.199
	p	.839	.605	.010	.960	.393	.212
R (2d:4d)	r	-.221	-1.44	-.212	.092	-.076	.044
	p	.140	.409	.163	.307	.701	.786
L/2d	r	-.180	-.305	-.454	.044	.118	-.143
	p	.233	.075	.002	.624	.551	.374
L/4d	r	-.026	-.247	-.396	-.052	.071	-.104
	p	.864	.153	.007	.566	.715	.517
L (2d:4d)	r	-.255	-.076	-.094	.165	.127	-.121
	p	.087	.665	.540	.064	.519	.452

R: right, L: left, HGS: hand grip strength

DISCUSSION

In this study, it could not be concluded which group caused the difference in hand width, hand length, hand grip strength, and 2d:4d measurements of fingers for Young and SAS parameters among male and female university students. However, it was determined that there was a moderately strong negative correlation between SAS and Right/2d, Right/4d, Left/2d, Left/4d parameters in male students.

Zhang et al.'s (10) meta-analysis study, which evaluated the results of 10 articles from 6 different countries in 2018, showed that approximately 30% of medical students were addicted to the internet. In addition to this study, Haroon et al. (11) observed in their study that most of the students participating in the study were internet addicts, and that women were more internet addicted than men. Shek and You (12) revealed that gender has nothing to do with internet addiction. According to the results of our study, in terms of internet addiction level of all students, 55% are normal (F: 39%, M: 14%), 19% are at risk addicts (F: 9%, M: 10%), 26% are in the addict group (F: 12%, E: 13%) was observed to be. With this result, we found that the prevalence of internet addiction in university students was approximately similar to the Zhang et al. meta-analysis. In addition, the similar rate of internet addiction results in both genders supported Shek and You's study. In the study where we evaluated physical therapy and nursing students, we think that the difficulty of the academic program related to the department, such as the students' busy schedules, long internships, and compulsory attendance, caused a decrease in the time spent on the internet, and gender did not affect this situation.

With the ability to use the Internet from desktop computers to mobile phones, it has become a great comfort to use it whenever and wherever you want. Kuyucu et al. (13) stated that mobile phones are mostly used in internet usage. Özsoy and Kulu (14) also found similar results for our country in their study. In our study, in terms of device preference for internet use, the phone was at the forefront for 82% of all participants (74% for men, 88% for women). In addition, in terms of device preference for internet use, 94% of normal addicts, 76% of risky addicts, and 65% of addicts were using phones.

In our study, it was determined that there was no statistically significant difference in terms of height, weight, BMI, dominant extremity, and device preference according to the addiction levels of the genders (Table 1). In our literature review, we could not find any studies on height, weight, dominant extremity and device preference according to the addiction level of the genders. However, regarding BMI, Canan et al., in a study conducted on 1938 students in 2013, showed that there was a relationship between BMI and internet addiction in Turkish adolescents, but it was reported that there was no difference between genders (15). Since the sample population in our study consisted of young healthcare professionals, we think that normal values were recorded in terms of BMI in both genders.

It is known that sex hormones in men and women are related to the 2d:4d ratio and that these lengths affect physiological, psychological and behavioral characteristics (16). Studies have found that low 2d:4d due to prenatal androgens is associated with alcohol addiction, substance addiction, and phone and computer game addiction in men (17,18). The 2d:4d marker, which we know can be easily included as a biomarker to understand the biological basis of excessive internet use, has been reported to regulate prenatal sex steroids, brain structure and function, and finger development during embryogenesis (19). In a study by Canan et al. (15), the right hand was associated with internet use disorder with lower 2D:4D values in men, and in another study by Kornhuber et al. (20), young men diagnosed with video game addiction had lower 2D:4D values compared to healthy controls. It was observed that the 4D result was obtained. In our study, we found that there was no difference regarding 2d:4d in both male and female individuals. We concluded that these parameters are decisive in investigating the relationship with addiction status, regardless of gender.

It is known in the literature that there is a relationship between finger length and hand grip strength (21). It has been found that dominant side grip strength decreases due to smartphone use (22). In our study, we concluded that there were significant differences in left hand length, right 4d, young, SAS in both male and female individuals, and that these parameters were decisive in investigating the relationship with addiction status, regardless of gender. We thought that the significant difference in left HGS in men was due to the muscle strength of men and that the parameters affected by muscle strength could not yield results in the difference parameters between genders. In addition, we think that the effect of the right 4d is on the fact that the phone is generally held with the right hand and the 2nd finger is generally fixed in the grip, while the 4th finger has the task of being mobile to control the thumb movements.

CONCLUSION

We have concluded that the scales accepted for phone and internet addiction in male and female individuals may be decisive in their gender relations rather than the 2d:4d finger ratios, as hand length, especially the right 4d, acts as a mobile device that provides control in phone use. In other words, we think that the biomechanical factor may be effective rather than the 2d:4d anthropometric measurement of addiction.

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REFERENCES

1. Rathbone AL, Prescott J. The use of mobile apps and SMS messaging as physical and mental health interventions: systematic review. *J Med Internet Res*. 2017;19:e295.
2. Öztürk Ö, Kalyoncu ÖA, Genç Y, et al. İnternet bağımlılığı: kliniği ve tedavisi. *Bağımlılık Derg*. 2007;8:36-41.
3. Young KS. Internet addiction: a new clinical phenomenon and its consequences. *Am Behav Sci*. 2004;48:402-15.
4. Dalbudak E, Evren C, Aldemir S, et al. Relationship of internet addiction severity with depression, anxiety, and alexithymia, temperament and character in university students. *Cyberpsychology Behav Soc Netw*. 2013;16:272-8.
5. Myers L, Van't Westeinde A, Kuja-Halkola R, et al. 2D:4D ratio in neurodevelopmental disorders: a twin study. *J Autism Dev Disord*. 2018;48:3244-52.
6. Kyriakidis I, Papaioannidou P. Epidemiologic study of the sexually dimorphic second to fourth digit ratio (2D:4D) and other finger ratios in Greek population. *Coll Antropol*. 2008;32:1093-8.
7. Açar G, Digilli B, Sağlam A, Çiçekcibaşı A. The relationship of the digit ratio (2D:4D) with body fat distribution and handgrip strength in medical students. *Cukurova Med J*. 2021;46:555-65.
8. Çakır Balta Ö, Horzum MB. The factors that affect internet addiction of students in a web based learning environment. *Ankara University Journal of Faculty of Educational Sciences (JFES)*. 2008;41:187-205.
9. Kwon M, Kim DJ, Cho H, Yang S. The Smartphone Addiction Scale: development and validation of a short version for adolescents. *PLoS ONE*. 2013;8:e83558.
10. Zhang MWB, Lim RBC, Lee C, Ho RCM. Prevalence of internet addiction in medical students: a meta-analysis. *Acad Psychiatry*. 2018;42:88-93.
11. Haroon MZ, Zeb Z, Javed Z, et al. Internet addiction in medical students. *J Ayub Med Coll Abbottabad*. 2018;30:S659-63.
12. Shek DTL, Tang VMY, Lo CY. Internet addiction in Chinese adolescents in Hong Kong: assessment, profiles, and psychosocial correlates. *ScientificWorldJournal*. 2008;8:776-87.
13. Kuyucu M. Use of smart phone and problematic of smart phone addiction in young people: "smart phone (colic)" university youth. *Glob Media J TR Ed*. 2017;7:328-59.
14. Özsoy F, Kulu M. Addiction in healthcare employees: examining the smoking, alcohol, internet, smartphone addiction, and attention deficit levels. *Genel Tıp Derg*. 2021;31:82-90.
15. Canan F, Yildirim O, Ustunel TY, et al. The relationship between internet addiction and body mass index in Turkish adolescents. *Cyberpsychology Behav Soc Netw*. 2014;17:40-5.
16. Tatar A, Özmen HE, Aksu F. Assessment of personality traits of young women by 2nd/4th digit ratio. *Nobel Med*. 2017;13:39-47.
17. Kornhuber J, Erhard G, Lenz B, et al. Low digit ratio 2D:4D in alcohol dependent patients. *PLoS ONE*. 2011;6:e19332.
18. Müller M, Brand M, Mies J, et al. The 2D:4D marker and different forms of internet use disorder. *Front Psychiatry*. 2017;8:213.
19. Hines M. Sex-related variation in human behavior and the brain. *Trends Cogn Sci*. 2010;14:448-56.
20. Kornhuber J, Zenses EM, Lenz B, et al. Low 2D:4D values are associated with video game addiction. *PLoS One*. 2013;8:e79539.
21. Günther CM, Bürger A, Rickert M, Schulz CU. Key pinch in healthy adults: normative values. *J Hand Surg Eur Vol*. 2008;33:144-8.
22. İnal EE, Demirci K, Çetintürk A, et al. Effects of smartphone overuse on hand function, pinch strength, and the median nerve. *Muscle Nerve*. 2015;52:183-8.



The High Suicide Rates at High Altitudes May Be Related to Divorce

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Abstract

Aim: Many studies have found that high altitudes are associated with suicide. Despite numerous studies in the literature, the mechanism by which high altitude increases suicide rates is not known. In this study, we investigated whether divorce affects the suicide rate at high altitudes.

Material and Method: Using publicly available data from the Turkish Statistical Institute (TUIK), the average altitude above sea level, suicide rate, and divorce rate of each province over the last 14 years were calculated. Divorce rates, suicide rates, and altitudes were statistically compared at the end of the study.

Results: The mean suicide rate did not differ according to altitude ($r=0.112$; $p=0.322$). The mean divorce rate differed according to altitude. The highest mean divorce rate was observed in the group with an altitude of less than 500 m ($p<0.001$). In the correlation analysis, it was found that altitude was negatively correlated with the divorce rate, divorce, and suicide rates were positively correlated, and in the regression analysis, high altitude and divorce rate increased the suicide rate (<0.05).

Conclusion: Our study suggests that divorced people in high-altitude areas are in the high-risk group for suicide and that mental health protective interventions, especially for this group, may be appropriate for prevention. In conclusion, this study is important, as it is the first to investigate the relationship between altitude, divorce, and suicide. Larger-scale studies in which individual factors were excluded are required.

Keywords: Altitude, divorce, suicide, family ties, geographical region

INTRODUCTION

Suicide is the voluntary ending of one's life. Its etiology is multifactorial. Suicide attempts may occur due to biological, sociological, and psychological reasons. Suicide is among the leading causes of death worldwide, with more deaths due to suicide than to malaria, Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS), breast cancer, war, and homicide. More than one in every 100 deaths (1.3%) in 2019 were the result of suicide. According to the World Health Organisation (WHO), 700,000 people died by taking their own lives in 2019 (1). It is estimated that suicidal acts are 10 times higher than this number. Suicide and suicide attempts have become a public health problem

in many countries because they leave severe traumas on the immediate environment and society. For this reason, every country is trying to develop various policies and measures to prevent suicide. Despite this, the number of people dying by suicide is increasing day by day. The biggest obstacle to early intervention is the lack of knowledge of the population at risk. Many studies have identified various risk factors that may be associated with suicide. The biggest risk factor is psychiatric diseases especially depressive disorder (2). The high suicide rate in some families indicates that the event may be genetically related (3). The concept of suicide has been handled from psychological, sociological, biological, and economic perspectives and various theories have been developed

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on its causes. When we look at sociological risks, it has been reported that weak social ties may constitute a risk for suicide. Other sociological risk factors include family discord, divorce, forced migration, inability to find a job, course failure, etc. (4). Most studies have focused on the biological and psychological causes of suicide. Recent studies have focused on natural environmental factors, such as altitude, temperature, and climatic factors. A study conducted in Türkiye found that high altitude and low temperature were associated with female suicide (5). A meta-analysis reported a positive relationship between high altitude and suicide in 17 of 19 studies (United States (n=11), Türkiye (n=2), Ecuador (n=1), Japan (n=1), South Korea (n=1), Austria (n=1), Italy (n=1), and one study that encompassed sixty-two nations.) (6). It is not known exactly which factors affect suicide rates at high altitudes. However, most studies conducted on the sociological causes of suicide reported that divorce was positively associated with suicide. Being divorced or separated is associated with a higher suicide risk than never being married, for both sexes. The separated have an odds ratio over five times as high as married do (7). Some studies have reported that divorce is negatively associated with suicide in some groups (8). Individual factors have been ignored in most studies. Although many studies have been conducted on which factors mediate the high suicide rate at high altitudes, no definite conclusion has been reached. In this study, we investigated whether the divorce rate mediates the suicide rate at high altitudes.

MATERIAL AND METHOD

Ethical approval for the study was obtained with the permission of the Karamanoğlu Mehmetbey University Ethics Committee, dated February 27, 2024, and numbered 01-2024/04. The data in this study were obtained from the web pages of the Turkish Statistical Institute (TUIK) (9). The suicide rate and divorce rate of all provinces in Türkiye (81 provinces) were calculated by taking the average of 14 years between 2009 and 2022. Crude suicide rate refers to the number of suicides per hundred thousand population (10). The crude divorce rate refers to the number of divorces per thousand population (11). The provinces were grouped at three different altitudes: 0-499m, 500-999m, and above 1000m (12). At the end of the study, divorce rate, suicide rate, and altitude were compared statistically.

Statistical Analysis

All data were analyzed in a computer environment using SPSS 25.0. The conformity of the data to a normal distribution was evaluated using the Kolmogorov-Smirnov test. ANOVA test was used to determine the differences between groups in the analysis of normally distributed continuous variables. The Post Hoc Tamhane test was used to evaluate differences between the groups. Pearson's Correlation test was used to analyze

the relationships between continuous variables. The correlation coefficient was interpreted according to the correlation coefficients reported by Sumbuloglu (2007) (Low=0.01-0.49; Medium=0.50-0.69; High=0.70-1.00) (13). Linear regression analysis was used to examine the factors predicting mean suicide rates. In regression analyses, autocorrelation was evaluated with Durbin-Watson, and multicollinearity was evaluated using tolerance and variance inflation factor (VIF). A statistical significance level of $p < 0.05$ was accepted in the study.

RESULTS

Changes in suicide and divorce rates in Türkiye by years are given in Figure 1.

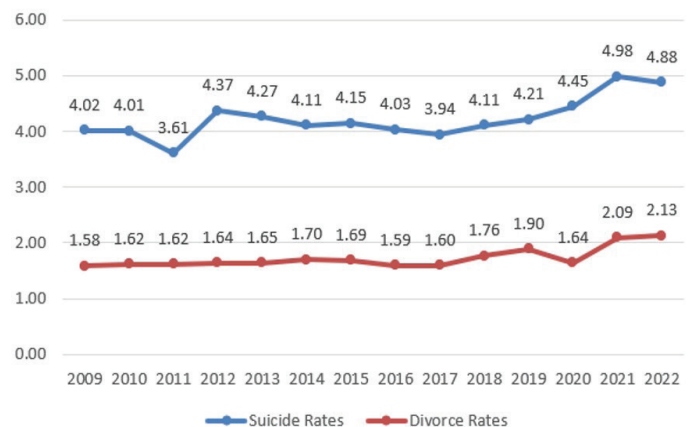


Figure 1. Changes in suicide and divorce rates by years (2009-2022)

The averages of suicide rates and divorce rates in all provinces between 2009 and 2022 are presented in Table 1.

When the correlation between altitude, suicide rates, and divorce rates of the provinces was analyzed, it was observed that there was a negative, moderate correlation between altitude and divorce rate, and a positive, weak correlation between suicide and divorce rates (Table 2).

The suicide rate averages did not differ according to altitude. However, the mean divorce rates differed between the groups, and the highest mean divorce rate was observed in the 0-499-meter altitude group ($p < 0.001$) (Table 3).

In the regression model established between the mean crude suicide rates and the mean altitude and divorce rates, it was determined that there was no autocorrelation (Durbin-Watson=1.797), there was no multicollinearity problem, and the standardized residuals of the variables fit a normal distribution. The model explained 16.1% of the change in mean crude suicide rate ($F=8.556$; Adj. $R^2=0.161$; $p < 0.001$). When the significance level of the β coefficient in the model was analyzed, it was observed that altitude made a positive ($t=3.053$; $p < 0.001$) and independent contribution to the model ($t=3.991$; $p < 0.001$) (Table 4).

Table 1. Altitude, average suicide rate (2009-2022) and average divorce rate (2009-2022)

Province name	Altitude (m)	Average suicide rates	Average divorce rates	Province name	Altitude (m)	Average suicide rates	Average divorce rates	Province name	Altitude (m)	Average suicide rates	Average divorce rates
Erzurum	1890	3.65	0.67	Kütahya	950	4.51	1.57	Kırklareli	209	5.02	1.87
Ardahan	1870	7.11	0.67	Mardin	938	3.25	0.47	Bursa	155	4.3	1.85
Kars	1768	5.94	0.6	Tunceli	914	9.62	1.62	Osmaniye	150	3.94	1.44
Hakkari	1748	4.04	0.2	Uşak	906	5.5	2.31	Düzce	146	3.32	1.78
Van	1727	4.37	0.37	Siirt	902	4.29	0.3	Balıkesir	139	5.15	2.07
Ağrı	1640	4.28	0.4	Iğdır	860	5.06	1.17	İstanbul	120	3.3	1.98
Bayburt	1556		0.65	Ankara	850	4.04	2.22	Hatay	85	2.85	1.52
Bitlis	1500	3.43	0.29	Gaziantep	843	3.77	1.42	Manisa	74	4.43	1.84
Muş	1404	5.7	0.29	Çorum	801	4.84	1.55	Aydın	64	7.03	2.27
Şırnak	1350	3.96	0.24	Kastamonu	798	5.11	1.2	Edirne	42	6.09	1.8
Yozgat	1301	3.38	1.47	Eskişehir	782	5.87	2.19	Antalya	39	4.93	2.72
Sivas	1285	4.37	1.2	Bolu	725	4.13	1.51	Sakarya	31	2.96	1.62
Nevşehir	1250	4.18	2.03	Çankırı	723	3.35	1.22	Adana	23	4.83	1.96
Niğde	1229	4.72	1.58	Kırkkale	700	4.63	2.07	Bartın	19	4.91	1.59
Erzincan	1214	4.07	1.25	Diyarbakır	670	4.77	0.56	Sinop	17	4.79	1.54
Gümüşhane	1153	1.76	0.65	Adıyaman	669	3.74	0.91	Tekirdağ	10	4.61	2.05
Bingöl	1151	5.39	0.55	Kilis	640	4.65	1.18	Trabzon	10	3.37	0.96
Kayseri	1071	5.06	1.93	Tokat	640	4.1	1.2	Zonguldak	10	4.93	1.81
Elazığ	1067	5.15	1.19	Muğla	625	6.21	2.58	Mersin	6	5.32	2.15
Karaman	1038	5.95	1.98	K.maraş	568	3.6	1.53	Rize	6	3.08	0.95
Isparta	1035	5.68	1.56	Batman	525	3.8	0.4	Giresun	5	3.12	1.32
Afyonkarahisar	1021	4.93	1.47	Artvin	520	3.18	1.01	Yalova	5	3.79	1.91
Konya	1016	4.12	1.77	Şanlıurfa	518	3.05	0.58	Samsun	4	4.21	1.52
Kırşehir	978	4.91	1.81	Bilecik	500	5.25	1.63	Çanakkale	3	5.42	1.84
Aksaray	975	3.6	2.12	Amasya	392	3.58	1.39	Kocaeli	3	3.5	1.81
Malatya	964	3.84	1.3	Denizli	354	6.23	2.38	Ordu	3	3.99	1.25
Burdur	950	6.45	1.67	Karabük	258	4.13	1.65	İzmir	2	4.98	2.77

Table 2. Correlation between altitude, average suicide rates, and average divorce rates of provinces

		Average suicide rates	Average divorce rates
Altitude (m)	r	0.112	-.546**
	p	0.322	<0.001
Average suicide rates	r	1	.288**
	p		0.010

** Pearson's correlation test

Table 3. Comparison of the average suicide rate and average divorce rate of provinces by altitude

	Altitude (m)	n	Mean	Std. Dev	Min	Max	p*	p1	p2	p3
Average suicide rates	0-499 (1)	30	4.40	1.04	2.85	7.03	0.758			
	500-999 (2)	28	4.61	1.33	3.05	9.62				
	1000 and above (3)	23	4.60	1.13	1.76	7.11				
Average divorce rates	0-499 (1)	30	1.79	0.43	0.95	2.77	<0.001	<0.05	<0.05	>0.05
	500-999 (2)	28	1.40	0.61	0.30	2.58				
	1000 and above (3)	23	1.00	0.62	0.20	2.03				

*ANOVA Test, p1=1 vs 2, p2=1 vs 3, p3=2 vs 3

Table 4. Effect of altitude and average divorce rate on predicting suicide rates of provinces

	Beta	Std. error	t	B	95.0% CI for B		Collinearity statistics	
					Lower bound	Upper bound	Tolerance	VIF
(Constant)		0.458	5.901*	2.705	1.792	3.617		
Altitude (m)	0.372	0.000	3.053*	0.001	0.000	0.001	0.714	1.400
Average divorce rates	0.487	0.226	3.991*	0.901	0.451	1.350	0.714	1.400

* Linear regression analysis

DISCUSSION

In our study, the suicide rate was found to be more related to the divorce rate in high-altitude areas than in low-altitude areas. According to our study, as the divorce rate increases in high-altitude areas, the suicide rate also increases. No studies in the literature have compared these three parameters: altitude, divorce rate, and suicide rate. Therefore, our study may lead to new research and contribute to the literature.

According to our study, there was no direct relationship between altitude and suicide rates. Several studies have investigated the relationship between altitude and suicide. In a meta-analysis, a positive relationship was found between high altitude and suicide rates in the majority of studies (6). The reason for the relationship between high altitude and suicide remains unknown. However, there are conflicting results for these reasons. A large-scale study conducted in China concluded that suicide rates were not directly related to the place of residence and that high suicide rates at high altitudes were related to low socioeconomic status (14). In contrast to this study, another study reported that suicide rates were still higher at high altitudes, even after excluding low socioeconomic levels, age, sex, and ethnic origin (15). Possible reasons for the lack of difference between the two variables in our study may be socioeconomic status, educational status, deficiency in keeping records, etc. However, suicide rate is not directly related to high altitude, suggesting that the increase in divorce rate at high altitude may mediate the increase in suicide rate.

A negative relationship was found between the divorce rate and altitude. The divorce rate was higher in provinces with low altitudes (0-499m) and lower in provinces with high altitudes (1000m and above).

The divorce rate was positively associated with the suicide rate in high-altitude areas. The fact that the divorce rate was positively associated with the suicide rate in high-altitude areas may be related to the fact that family ties are culturally strong in high-altitude areas and isolation as a result of divorce. The finding that the divorce rate was lower in high-altitude areas supports our hypothesis that the importance given to families is higher. There are no studies in the literature that investigate the relationship between altitude and divorce. In this respect, our study may lead to further research.

In this study, the positive relationship between the divorce rate and the suicide rate is consistent with the literature

(16-18). Although the positive relationship between divorce and suicidal behavior has been documented in many studies, the reasons for mediating this relationship are not fully known (19). Understanding the reason for the relationship between divorce and suicidal behavior and the conditions that play a role is important for the identification of the population at risk of suicide, screening, and early intervention. The fact that industrialization, urbanization, and education levels are higher in low-altitude provinces than in high-altitude provinces may have decreased the suicide rate as a result of divorce. The fact that divorces with religious marriages, which do not have legal validity in high altitude and rural areas, are not reflected in the statistics, on the other hand, traditional social pressures on marriage are higher in rural areas may have led to these results. In addition, the higher divorce rate in low-altitude areas may indicate culturally weak family ties. This may explain why the importance given to the family in low-altitude areas may be less than in high-altitude areas, and therefore, the divorce rate may have less effect on the suicide rate.

Our study had some limitations. First, individual factors such as educational status, socioeconomic status, age, and gender, which are confounding factors, were not considered. Provinces located at the same altitude but in different geographical regions were not compared. In Türkiye, death records are kept through the "Death Notification System" of the Ministry of Health. The causes of death entered into this system may be incomplete, which may make the number of suicides appear different than it is. In addition, data from only one country were evaluated. It should be taken into consideration that there may be cultural and behavioral differences between regions within the country

CONCLUSION

The relationship between altitude and suicide is an emerging science and there is a small but growing literature suggesting that altitude is associated with increased suicide risk. This study suggests that divorce at high altitudes is not associated with suicide at the same rate as divorce at low altitudes, that divorced people at high altitudes are in the high-risk group for suicide, and that mental health interventions, especially those targeting this group, may be appropriate for prevention. In conclusion, this study is important, as it is the first to investigate the relationship between altitude, divorce, and suicide. Larger-scale studies in which individual factors were excluded are required.

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REFERENCES

1. WHO. Suicide in the world: global health estimates. 2019 <https://www.who.int/publications/i/item/9789240026643> access date: 06.05.2024
2. Baldessarini RJ, Tondo L, Pinna M, et al. Suicidal risk factors in major affective disorders. *Br J Psychiatry*. 2019;215:621-6.
3. Nordentoft M. Prevention of suicide and attempted suicide in Denmark. *Dan Med Bull*. 2007;54:306-69.
4. Poyraz T, Çalışkan A. A sociological analysis of Turkey's suicide phenomenon. *itobiad*. 2019;8:2957-74.
5. Asirdizer M, Kartal E, Etli Y, et al. The effect of altitude and climate on the suicide rates in Turkey. *J Forensic Leg Med*. 2018;54:91-5.
6. Brown A, Hellem T, Schreiber J, et al. Suicide and altitude: a systematic review of global literature. *Public Health Nurs*. 2022;39:1167-79.
7. Øien-Ødegaard C, Hauge LJ, Reneflot A. Marital status, educational attainment, and suicide risk: a Norwegian register-based population study. *Popul Health Metr*. 2021;19:33.
8. Yang X, Liu L, Li R. How marital events explain the suicide rate among Chinese. *Plos one*. 2023;18:e0286961.
9. TUIK. Turkish Statistical Institute (TUIK) of the Republic of Turkey. <https://www.tuik.gov.tr/> access date 06.05.2024.
10. Turkish Statistical Institute (TUIK). Ölüm ve ölüm nedeni istatistikleri, 2022. <https://data.tuik.gov.tr/Bulten/Index?p=Olum-ve-Olum-Nedeni-Istatistikleri-2022-49679> access date 09.02.2024.
11. Turkish Statistical Institute (TUIK). Evlenme ve boşanma istatistikleri, 2022. <https://data.tuik.gov.tr/Bulten/Index?p=Evlenme-ve-Bosanma-Istatistikleri-2022-49437> access date 09.02.2024.
12. Blogarti. Türkiye'deki illerin rakım sıralaması. <https://www.blogarti.com/illerin-rakim-siralamasi.html> access date 09.02.2024.
13. Sümbüloğlu K, Akdağ B. Regresyon Yöntemleri ve Korelasyon Analizi, Hatiboğlu Yayınları, Ankara, 2007;12.
14. Gong S LC, Xiao K. Spatial-temporal characteristics and relations with economy of suicide phenomenon in China from 2000 to 2018. *Tropical Geography*. 2023;43:1760-76.
15. Kim J, Choi N, Lee Y-J, et al. High altitude remains associated with elevated suicide rates after adjusting for socioeconomic status: A study from South Korea. *Psychiatry Investig*. 2014;11:492-4.
16. Aksoy T, Yerlikaya B. Divorce and suicide: a subnational analysis in Turkey. *Topics in Middle Eastern & North African Economies: Proceedings of the Middle East Economic Association*. 2021;23:54-77.
17. Rihmer Z, Rihmer A, Beltezcki Z. Psycho-social correlates of suicidal behaviour. *Neuropsychopharmacol Hung*. 2022;24:162-9.
18. Jimenez A, Santed-Germán M-A, Ramos V. Google searches and suicide rates in Spain, 2004-2013: correlation study. *JMIR Public Health Surveill*. 2020;6:e10919.
19. Edwards AC, Ohlsson H, Salvatore JE, et al. Divorce and risk of suicide attempt: a Swedish national study. *Psychol Med*. 2023 Dec 12. doi: 10.1017/S0033291723003513. [Epub ahead of print].



Evaluation of ChatGPT as a Multiple-Choice Question Generator in Dental Traumatology

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Abstract

Aim: This study aims to evaluate the ability of ChatGPT-4 to generate clinical case-based multiple-choice questions in dental traumatology.

Material and Method: International Association of Dental Traumatology guidelines for the management of traumatic dental injuries were introduced to ChatGPT-4 as an information source and ChatGPT-4 was prompted to generate 20 questions in fractures and luxations, avulsion of permanent teeth, injuries in the primary dentition. Sixty questions in total were generated by ChatGPT and the questions were evaluated by 2 endodontists using a 3-point scale. The One-way analysis of variance and Post Hoc Tukey test were used to analyze the data and the significance was $P < 0.05$.

Results: The average time to generate 20 questions was 1 min 55 sec. It was noted that 52% of the questions were usable without modification or with minor changes, while 28% were incorrect or completely useless.

Conclusion: Despite the flaws, ChatGPT can be useful for creating multiple-choice questions in dental traumatology after a rigorous evaluation, elimination, and development procedure.

Keywords: Artificial intelligence, clinical practice guidelines, dental education, endodontics, treatment planning

INTRODUCTION

Dental education is a meticulously structured journey that prepares students for the challenging responsibilities of the occupation. It combines rigorous academic coursework with practical training. The goal is to ensure that upon graduation, these students are academically and practically competent. Dental traumatology (DT) education is an essential component of dental school curricula, addressing the diagnosis, treatment, and prevention of trauma to the teeth and surrounding oral structures. Moreover, DT is one of the important topics of both endodontics and pediatric dentistry, as it is a wide area ranging from an enamel fracture to tooth avulsion and may require complex treatments depending on the diagnosis. Traumatic dental injuries, often seen in sports, accidents, or falls, require immediate and effective intervention to save teeth and maintain oral function. By integrating DT into dental education, future dentists are equipped with the necessary skills and knowledge to manage these injuries effectively.

Assessment is a crucial part of understanding students' competence. Multiple choice questions (MCQs) are a common method of assessment of medical examinations because they are objective, standardized, and time-efficient (1). Preparation of MCQs that evaluate both the application and interpretation of knowledge rather than the recall of information only can be challenging (2). Furthermore, it was found that students were inclined to engage more thoroughly in their studies when faced with test questions that necessitated advanced analytical thinking (3). The university staff has various tasks including treatment of patients, research, and teaching, etc (4). Therefore, reducing the workload through automation of appropriate tasks can be useful for the productive use of time and to avoid staff burnout.

Education is among the fields that potentially be revolutionized by artificial intelligence (AI) (5). AI is a rapidly developing phenomenon that includes many different technologies, such as machine learning and natural language processing. AI technologies can assist

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healthcare professionals by automating tasks that are repetitive and consume a lot of time (6). Large Language Models (LLMs) are advanced AI systems that emulate human language processing skills by training on extensive datasets. These models are capable of comprehending and generating the content, allowing them to perform tasks like article generation and answering questions in a near-human manner (7,8).

ChatGPT (Chat Generative Pre-Trained Transformer) (OpenAI, San Francisco, CA, USA) is a promising LLM, utilizing deep learning AI techniques to generate articulate and human-resembling texts (9). Although studies (10-13) questioning the ability of ChatGPT to answer questions correctly related to different fields of dentistry and its use as an information source are increasing, it has been found in different studies that it can produce texts containing unrealistic and misleading information, which is called "hallucination". ChatGPT's ability to generate questions has also been evaluated in various studies (14,15) and different results have been reported. Cheung et al. (14) found that ChatGPT can generate medical MCQs with comparable quality to university staff. ChatGPT-3.5, the older version, was found to generate suboptimal MCQs without distractor options in dermatology (15). ChatGPT-4, as the newest version, has features that its predecessors did not have, such as enabling image and document input and internet access. Thus, when a text is uploaded as a document, it can understand, summarise, and answer questions about that text (16,17). Given these features, it can be speculated that ChatGPT-4 can produce high-quality and reliable MCQs based on an existing text. Deriving questions by introducing documents representing consensus in dentistry, such as position statements of dental associations and clinical guidelines, into ChatGPT-4 can shorten the question preparation time and improve the quality of the evaluated questions. Thereby, the production of texts containing unrealistic references and information can be prevented.

To the best of our knowledge, there is no study in the literature questioning the ability of LLMs such as ChatGPT to generate questions in any other field of dentistry. Thus, the aim of this study is to evaluate the ability of ChatGPT-4 to generate clinical case-based MCQs in DT. The null hypothesis was as follows: There is no association between the type of dental trauma (fractures and luxations, avulsion of permanent teeth, injuries in the primary dentition) and the usability of MCQs generated by ChatGPT-4.

MATERIAL AND METHOD

The study was conducted under the Declaration of Helsinki. Since the study had no human subjects involved, ethical approval was not required. ChatGPT-4 was logged in on 14 January 2024. International Association of Dental Traumatology (IADT) guidelines for the management

of traumatic dental injuries represent the consensus of experts in the field and are up-to-date as a resource prepared by the working group of the IADT as a result of a comprehensive literature review and approved by the board of directors (18-21). In addition, since these are open-access articles, they were used as a source to derive questions in our study.

The first part of the guidelines, "fractures and luxations", was uploaded to the ChatGPT console and the following prompt was written exactly as follows: "Can you write a full set of 20 multiple-choice questions based on the document I provided, each with 5 options and focusing solely on clinical case scenarios in dental traumatology? An answer key is required at the end." (Figure 1). Then the second section, avulsion of permanent teeth, and the third section, injuries in the primary dentition, were uploaded in separate tabs and questions were generated with the same prompt. Question generation times for all sections were noted and as a result, 60 questions were obtained, and these questions were copied and saved. The two reviewers jointly assessed and scored the questions based on the guidelines. In case of disagreement, the decision of a third reviewer was decisive. In the evaluation, the evaluation criteria used in a similar study by Ngo et al. (22) was adopted (Table 1).

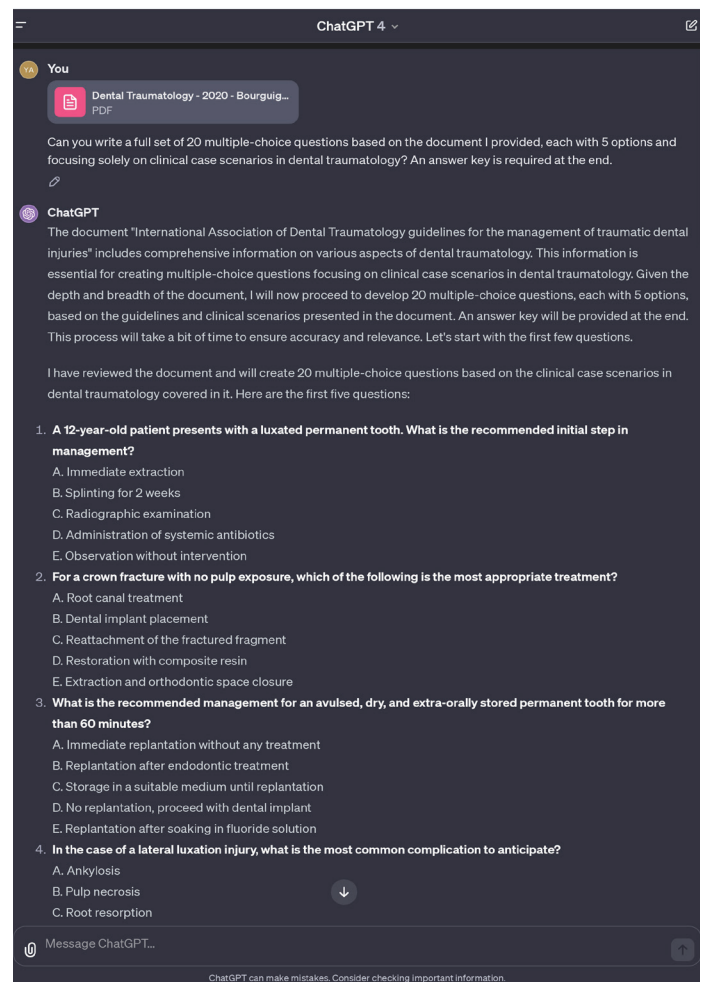


Figure 1. Generation of multiple-choice questions via ChatGPT-4

Table 1. Scoring definition

Score	Description
1	Questions and answers were correct and may be used with only minor formatting
2	Questions and answers would require substantial modifications to be appropriate
3	Answers were incorrect or significantly misleading

Statistical Analysis

The statistical analysis was performed via MiniTab 17 (Minitab Inc., PA, USA). The normality of the data was assessed with Ryan-Joiner test and the normal distribution of the data was confirmed. One-way analysis of variance (ANOVA) and Post Hoc Tukey test were performed. A significance level of $P < 0.05$ was used to determine statistical significance.

RESULTS

The mean values and standard deviations of each group are

presented in Table 2. Average score of all DT questions was 1.55. "Avulsion of permanent" teeth demonstrated the best score followed by "injuries in the primary dentition" and "fractures and luxations" respectively. The difference between "fractures and luxations" and "avulsion of permanent teeth" was statistically significant ($P = 0.029$). After the prompt was input, the average time to generate 20 questions was 1 min 55 sec. It was noted that 52% of the questions were usable without modification or with minor changes, while 28% were incorrect or completely useless.

Table 2. Scores of questions by topic

Topic	Number of questions	Mean	Standard deviation	Score-1	Score-2	Score-3
Fractures and luxations ^A	20	2.00	0.858	7	6	7
Avulsion of permanent teeth ^B	20	1.35	0.587	14	5	1
Injuries in the primary dentition ^{A,B}	20	1.95	0.999	10	1	9
Dental traumatology	60	1.55	0.790	31 (52%)	12 (20%)	17 (28%)

Different letters indicate statistically significant difference ($P < 0.05$)

DISCUSSION

The null hypothesis was that there is no association between the type of dental trauma and the usability of MCQs generated by ChatGPT-4. The null hypothesis can be partially rejected as the analysis revealed a significant association between the type of dental trauma and question usability.

It was found that all the questions were within the scope of the subject. It was also concluded that there were no spelling or grammatical errors in the questions and all questions were understandable. The ability to prepare 20 questions within the scope of the subject in a short time such as an average of 1 min 55 sec shows that ChatGPT is a potential tool that can save time for the faculty members. In agreement with our study, Cheung et al. (14) also reported that ChatGPT prepared 50 medical MCQs in 20 min 25 sec, which is much faster compared to the professional staff who prepared 50 medical MCQs in 211 min 33 sec.

The reason why questions with case scenarios were included in the study is that it is important to measure the usability of information in addition to the recall of information. The common deficiency observed in some of the questions produced by ChatGPT was that the case stories were quite superficial and lacked detail. For example, one of the prepared questions was as follows: "A 15-year-old patient presents with a luxated and non-responsive tooth. The most likely diagnosis is:..." It can be expected that more relevant and high-quality questions would contain more details about the cases. This may make it necessary to revise the ChatGPT questions rather

than using them as they are. Therefore, it is not possible to claim that all the questions produced by ChatGPT are high quality clinical case-based questions, although the dental trauma questions are within the context and relevant.

When preparing a case question, depending on the question, the presence of periapical X-rays or intraoral photographs may be essential or may improve the quality of the question. Unlike its predecessors, ChatGPT-4 has the feature of creating images as instructed and within the limits of skill. However, it is apparent that ChatGPT-4's inability to create medical images reduces the question quality and this is a deficiency in its use for MCQ preparation. Considering the pace of development of LLMs, it may be useful to re-evaluate the usability of ChatGPT and other language models in dental education when more advanced versions become available.

ChatGPT and other LLMs producing false information and references have been observed before in various studies (10-13,22) in various fields. In this study, to avoid this situation, which is called hallucination, and to obtain questions based on accurate and up-to-date information, IADT's guidelines were introduced to ChatGPT, and it was aimed to prepare the questions within the framework of these guidelines. The results showed that introducing sources to ChatGPT did not prevent completely the production of text containing false information.

In previous studies (14,22) in which MCQs were prepared based on a selected source, the researchers introduced the information source to ChatGPT by selecting a text, copying and pasting it into ChatGPT. The reason for using ChatGPT-4 in the present study is that, unlike its

predecessors and other LLMs, it allows documents to be preloaded as files. Thus, in this study, unlike the previous studies, sources were directly uploaded as files. The direct uploadability of the source on which the questions are based may offer ease of use.

According to the results of this study, only 52% of the questions produced by ChatGPT can be used without major revision. Ngo et al. (22) reported that only 32% of the MCQs generated by ChatGPT-3.5 in pathology were correct. However, it should be taken into consideration that the previous version of ChatGPT was used in the study of Ngo et al. However, these results are in line with our study in terms of the presence of completely wrong or useless questions.

CONCLUSION

This is the first study to evaluate the question preparation ability of an LLM in dentistry and evaluated the MCQs produced by ChatGPT-4 on DT and considered ChatGPT-4 as a potential question bank. Although ChatGPT has the potential to be used as a question bank in dental education, it can only remain as a "potential" unless the production of misinformation and the lack of creative medical writing are completely eliminated. The questions produced by ChatGPT can only be used in their current form after a serious evaluation and revision.

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REFERENCES

1. Javaeed A. Assessment of higher ordered thinking in medical education: multiple choice questions and modified essay questions. *MedEdPublish*. 2018;7:128.
2. Scully D. Constructing multiple-choice items to measure higher-order thinking. *PARE*. 2019;22:4.
3. Scouller K. The influence of assessment method on students' learning approaches: multiple choice question examination versus assignment essay. *Higher Education*; Dordrecht. 1998;35:453-72.
4. Rao SK, Kimball AB, Lehrhoff SR, et al. The impact of administrative burden on academic physicians: results of a hospital-wide physician survey. *Acad Med*. 2017;92:237-43.
5. Chen L, Chen P, Lin Z. Artificial intelligence in education: a review. *IEEE Access*. 2020;8:75264-78.
6. Cardoso MJ, Houssami N, Pozzi G, Séroussi B. Artificial intelligence (AI) in breast cancer care-leveraging multidisciplinary skills to improve care. *Artif Intell Med*. 2022;123:102215.
7. Abd-Alrazaq A, AlSaad R, Alhuwail D, et al. Large language models in medical education: opportunities, challenges, and future directions. *JMIR Med Educ*. 2023;9:e48291.
8. Mesko B, Topol EJ. The imperative for regulatory oversight of large language models (or generative AI) in healthcare. *NPJ Digit Med*. 2023;6:120.
9. Fatani B. ChatGPT for future medical and dental research. *Cureus*. 2023;15:e37285.
10. Giannakopoulos K, Kavarella A, Stamatopoulos V, Kaklamanos E. Evaluation of generative artificial intelligence large language models ChatGPT, Google Bard, and Microsoft Bing Chat in supporting evidence-based dentistry: a comparative mixed-methods study. *J Med Internet Res*. 2023;25:e51580.
11. Acar AH. Can natural language processing serve as a consultant in oral surgery?. *J Stomatol Oral Maxillofac Surg*. 2024;125:101724.
12. Suarez A, Diaz-Flores Garcia V, Algar J, et al. Unveiling the ChatGPT phenomenon: evaluating the consistency and accuracy of endodontic question answers. *Int Endod J*. 2024;57:108-13.
13. Ali K, Barhom N, Tamimi F, Duggal M. ChatGPT-A double-edged sword for healthcare education? Implications for assessments of dental students. *Eur J Dent Educ*. 2024;28:206-11.
14. Cheung BHH, Lau GKK, Wong GTC, et al. ChatGPT versus human in generating medical graduate exam multiple choice questions-A multinational prospective study (Hong Kong S.A.R., Singapore, Ireland, and the United Kingdom). *PLoS One*. 2023;18:e0290691.
15. Ayub I, Hamann D, Hamann CR, Davis MJ. Exploring the potential and limitations of chat generative pre-trained transformer (ChatGPT) in generating board-style dermatology questions: a qualitative analysis. *Cureus*. 2023;15:e43717.
16. Kim HW, Shin DH, Kim J, et al. Assessing the performance of ChatGPT's responses to questions related to epilepsy: a cross-sectional study on natural language processing and medical information retrieval. *Seizure*. 2024;114:1-8.
17. Spallek S, Birrell L, Kershaw S, et al. Can we use ChatGPT for mental health and substance use education? Examining its quality and potential harms. *JMIR Med Educ*. 2023;9:e51243.
18. Bourguignon C, Cohenca N, Lauridsen E, et al. International Association of Dental Traumatology guidelines for the management of traumatic dental injuries: 1. fractures and luxations. *Dent Traumatol*. 2020;4:314-30.
19. Levin L, Day PF, Hicks L, et al. International Association of Dental Traumatology guidelines for the management of traumatic dental injuries: general introduction. *Dent Traumatol*. 2020;4:309-13.
20. Fouad AF, Abbott PV, Tsilingaridis G, et al. International Association of Dental Traumatology guidelines for the management of traumatic dental injuries: 2. avulsion of permanent teeth. *Dent Traumatol*. 2020;36:331-42.
21. Day PF, Flores MT, O'Connell AC, et al. International Association of Dental Traumatology guidelines for the management of traumatic dental injuries: 3. injuries in the primary dentition. *Dent Traumatol*. 2020;36:343-59.
22. Ngo A, Gupta S, Perrine O, et al. ChatGPT 3.5 fails to write appropriate multiple choice practice exam questions. *Acad Pathol*. 2023;11:100099.



Distance Parameter Values of Calcaneus and their Performance for Gender Estimation

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Abstract

Aim: The calcaneus has a significant role in the foot due to its location. It is used together with the pelvis and skull bones in gender determination. In this study, it was aimed to determine the morphometric characteristics of the calcaneus and determine the suitability of these measurement locations for gender estimation.

Material and Method: In the study, seven measurements were taken bilaterally from 1,080 lateral foot radiographs of 540 individuals aged 20-65 years. For foot bone height (FBL), the distance between the anterior end of the distal phalanx of the most distal toe and the most posterior end of the foot was taken, while for maximum calcaneal length (maxCaL), the distance between the anterior end of the calcaneus and the posterior end of the calcaneus was taken. SPSS 21 program was used for statistical analyses and the ratio of gender prediction performances was examined by Receiver operating characteristic (ROC) analysis.

Results: All length measurements were higher in males than females ($p < 0.05$), and foot bone height (FBL) ($p = 0.035$) and maximum calcaneus height (maxCaH) ($p = 0.007$) were higher on the right side than on the left side. The study also found a weak negative correlation between age and the right-sided medial calcaneus length parameter (rmedCaL) and strong correlations between certain measurements. Foot bone length (FBL) was found to have the highest accuracy in predicting gender (AUC=0.913).

Conclusion: The findings provide useful information for forensic cases, provide reference data for diagnosis and treatment processes in the clinic, and provide data for the development of machine learning software that can be used in medical and forensic cases.

Keywords: Calcaneus, forensic science, gender prediction, radiology, receiver operating characteristic analysis

INTRODUCTION

The feet carry and transfer the weight of the body to the ground throughout life and have anatomical features that do not require any auxiliary organs to fulfill their function (1). The calcaneus, one of the parts of the foot in contact with the ground, is the largest, longest, and most robust of the seven tarsal bones in the foot and is a roughly box-shaped bone that forms the heel at the back of the foot. It has complex contours and joint surfaces (2,3).

Due to its shape and position, the calcaneus plays a major role in transmitting force between the body and the ground. It plays a critical role in weight bearing. Due to its complexity and multiple joints connecting the ankle and hindfoot, disruption of the calcaneal anatomy can alter the biomechanics of the foot and lower extremities (4). In some pathologic conditions, changes in the morphometric characteristics of the calcaneus may be observed. In such cases, normal morphometric values of the calcaneus may guide the diagnosis and treatment processes (5).

Due to natural disasters, tragic accidents, terrorist attacks, and homicides, victims and their bodies can become unrecognizable. Identification of the body is particularly difficult in cases where the body has been decomposed, mutilated, or burned (6). One of the important fields of anthropology, and forensic anthropology in particular, is the identification of individuals. In the identification process, the age, race, and gender of the person are important. Therefore, knowing the gender of the person is quite important in terms of reducing the result set in the identification process (7,8).

Although the identification by DNA analysis is highly accurate, it is not practical to use this method in complex cases with a large number of cases due to its cost and time-consuming nature (8,9). Although the pelvis and skull bones used to estimate gender from bone have a high accuracy rate, other bones can be used in case of deterioration and fragmentation (10). One of these bones, the calcaneus, is often evaluated in forensic anthropology.

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The calcaneus can withstand high tensile forces due to its shape and the density of its trabeculae. It is a bone that is more protected against external factors since it is constantly in shoes and socks in daily life (11,12).

The objective of this study was to measure the length parameters of the calcaneus from lateral radiographs of the foot in a Central Anatolian population and to determine the effectiveness of these values for gender prediction.

MATERIAL AND METHOD

The study was conducted with a retrospective design with the approval of Necmettin Erbakan University Drug and Non-Medical Device Research Ethics Committee dated 04.02.2022 and numbered 2022/3632. Bilateral comparative foot radiography images (RI) of 8,001 people who applied to the Department of Radiology between 2018 and 2021 were scanned in the PACS (Picture Archiving and Communication System) archive system. The number of participants for this study was determined by G*Power (3.9.1) analysis based on the Agoada 2018 study (13). Images were randomly selected from PACS by two investigators according to the criteria. RI images of healthy individuals without any pathology in the foot region were included in the study. Patients with fractures, trauma or bone pathology in the tarsal, metatarsal bones and phalanges, structural defects, previous surgical intervention, aged 20 years or younger, and RI defects were excluded from the study. A total of 540 people between the ages of 20 and 65, 137 (25.4%) men and 403 (74.6%) women, who met these criteria were included in the study. The individuals included in the study (20-29 years, 30-39 years, 40-49 years, 50-59 years, and 60-65 years) were divided into age groups (Table 1). Seven distance measurements were made on the lateral RI of the foot (Figure 1). Measurements were taken three times by the same person at certain date intervals and the average values were used.

Table 1. Classification of the study population into five different groups according to age

		N	%
Sex	Male	137	25.4
	Female	403	74.6
Age groups	20-29	45	8.3
	30-39	126	23.3
	40-49	157	29.1
	50-59	177	32.8
	60-65	35	6.5

N: number of individuals

Definitions of Measurements

Foot bone height (FBH): The vertical distance between the line passing between the calcaneus and the caput os metatarsale-I and the highest point of the talus was measured (14) (Figure 1a).

Foot bone length (FBL): The distance between the anterior end of the phalanx distalis of the most distal finger (1st

or 2nd finger) and the most posterior end point of the foot was measured (15) (Figure 1b).

Maximum calcaneus length (maxCaL): The distance between the anterior extreme point of the calcaneus and the posterior extreme point was measured (16) (Figure 1c).

Medial calcaneus length (medCaL): The distance between the point where the anterior border of the lateral surface of the calcaneus begins to curve upward and the most posterior point of the tuber calcanei was measured (13) (Figure 1d).

Minimum calcaneus height (minCaH): The distance between the deepest point behind the facies articularis talaris posterior of the calcaneus and the highest point of the lower border of the lateral surface in front of the tuber calcanei was measured (13) (Figure 1e).

Calcaneus anterior facet height (CaAFH): On the anterior face of the calcaneus, the minimum distance between the upper and lower borders of the articular surface for cuboid on calcaneum was measured (16) (Figure 1f).

Maximum calcaneus height (maxCaH): The perpendicular distance between the line extending distally from the plantar aspect of the tuber calcanei parallel to the long axis of the calcaneus and the highest point of the anterior talar articular posterior surface was measured (13) (Figure 1g).

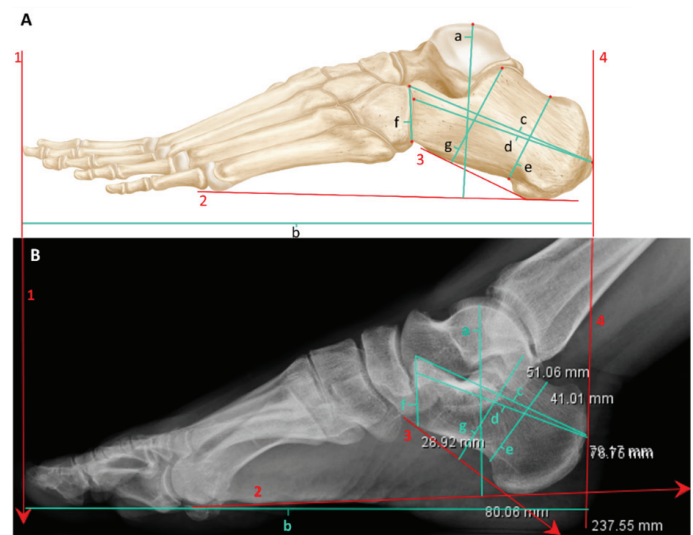


Figure 1. Measurements in the study (1A: Schematic view, 1B: PACS image, 1: line through the most anterior point of the foot, 2: contact surface, 3: parallel drawn on the lower surface of the calcaneus, 4: line through the most posterior point of the foot, 1a: foot bone length, 1b: foot bone height, 1c: maximum calcaneus length, 1d: medial calcaneus length, 1e: minimum calcaneus height, 1f: calcaneus anterior facet height, 1g: maximum calcaneus height)

Statistical Analysis

Statistical analysis of the study was performed with the IBM SPSS Statistics 21.0 (SPSS, V21; IBM Corp) program. The conformity of the data to normal distribution was analyzed with Kolmogorov–Smirnov test. The relationship between genders and ages was evaluated by the Chi-square analysis. Independent t-test was used to separate

and evaluate the measurements according to gender. The One-Way ANOVA-Tukey test was used for the evaluation between age groups. All measurements were analyzed with a dependent t-test between the right and left sides. Receiver operating characteristic (ROC) analysis was also performed to evaluate the suitability of gender prediction from the measured parameters. Analysis results were presented as Mean±SD for quantitative data and percentage (frequency) values for categorical data. The level of significance was taken as $p < 0.05$ in statistical analysis.

RESULTS

The minimum (min.), maximum (max.), mean, and standard deviation (SD) values of the right and left side and gender measurement data obtained in the study are given in Tables 2,3. Comparing the right and left sides of our measurement data, FBH ($p=0.035$) and maxCaH ($p=0.007$) values were found to be statistically significantly higher on the right side (Table 3).

All of the distance measurements made on the right and left sides were statistically significantly greater in men ($p < 0.05$) (Table 3).

Table 2. Minimum, maximum and mean values for all parameters

	Right			Left			P
	Min.	Max.	Mean±SD	Min.	Max.	Mean±SD	
FBH	54.63	98.8	83.29±6.43	62.97	99.82	82.96±6.27	0.035*
FBL	129.56	313.45	242.04±18.63	202.38	360.63	242.87±18.08	0.105
maxCaL	27.92	108.25	83.13±6.96	71.17	109.42	83.22±5.96	0.566
medCaL	35.14	100.5	76.86±6.16	43.26	100.77	76.79±5.98	0.633
minCaH	26.39	78.3	39.57±4.27	27.73	68.71	39.43±4.06	0.279
CaAFH	18.69	37.75	25.73±2.7	17.23	45.49	25.76±3.01	0.798
maxCaH	24.76	61.34	46.71±3.93	35.19	59.94	46.43±3.75	0.007*

Min.: minimum value, Max.: maximum value, SD: standard deviation value, FBH: foot bone height, FBL: foot bone length, maxCaL: maximum calcaneus length, medCaL: medial calcaneus length, minCaH: minimum calcaneus height, CaAFH: calcaneus anterior facet height, maxCaH: maximum calcaneus height, *0.05 significance level

Table 3. Comparison of the measurements according to gender

	Male (N=137)			Female (N=403)			p	
	Min.	Max.	Mean±SD	Min.	Max.	Mean±SD		
Age	20	65	42.29±11.48	20	65	43.81±10.46	0.174	
Right	FBH	64.24	98.88	89.07±5.97	54.63	97.42	81.33±5.31	<0.001*
	FBL	167.39	313.45	261.27±16.89	129.56	299.55	235.5±14.15	<0.001*
	maxCaL	77.25	108.25	89.94±5.58	27.92	98.85	80.81±5.76	<0.001*
	medCaL	71.88	100.5	83.26±5.29	35.14	90.32	74.69±4.77	<0.001*
	minCaH	33.92	53.32	42.89±3.57	26.39	78.3	38.44±3.88	<0.001*
	CaAFH	21.26	34.82	27.47±2.76	18.69	37.75	25.14±2.40	<0.001*
	maxCaH	42.03	61.34	50.58±3.61	24.76	57.07	45.4±3.07	<0.001*
Left	FBH	73.54	99.82	89.03±5.93	62.97	94.58	80.89±4.89	<0.001*
	FBL	225.18	315.2	261.81±15.13	202.38	360.63	236.43±14.03	<0.001*
	maxCaL	74.73	109.42	89.7±5.6	71.17	98.68	81.02±4.22	<0.001*
	medCaL	72.8	100.77	83.02±5.05	43.26	90.36	74.66±4.64	<0.001*
	minCaH	35.57	68.71	43.21±4.2	27.73	47.2	38.15±3.1	<0.001*
	CaAFH	19.38	34.15	27.53±2.74	17.23	45.49	25.16±2.86	<0.001*
	maxCaH	35.19	59.94	50.02±3.72	36.37	56.16	45.22±2.89	<0.001*

N: number of individuals, Min: minimum value, Max: maximum value, SD: standard deviation value, FBH: foot bone height, FBL: foot bone length, maxCaL: maximum calcaneus length, medCaL: medial calcaneus length, minCaH: minimum calcaneus height, CaAFH: calcaneus anterior facet height, maxCaH: maximum calcaneus height, *0.05 significance level

Examining the relationship between the length measurements of the calcaneus between age groups, it was seen that the parameter right calcaneus anterior facet height (rCaAFH) had a significant difference between age groups ($p=0.026$). Nevertheless, none of the parameters, including rCaAFH, showed a regular increase or decrease with age.

Examining the correlation between the data on the right

side, it was seen that all length measurements had a strong positive correlation among themselves ($p < 0.05$) (Table 4). When the correlation between the data on the left side was examined, a positive correlation was observed between all length measurements as on the right side ($p < 0.05$). While the correlation between left foot bone height (lFBH) and left foot bone length (lFBL) was weaker ($p < 0.05$, $r=0.562$), the correlation between the remaining data was found to be strong (Table 4).

Table 4. Correlation of the data of the parties within themselves										
		AGE	rFBH	rFBL	rmaxCaL	rmedCaL	rminCaH	rCaAFH	rmaxCaH	
rmaxCaH	r	.041	.651**	.603**	.579**	.558**	.573**	.392**	1	
	p	.343	.000	.000	.000	.000	.000	.000		1
rCaAFH	r	.059	.367**	.427**	.418**	.441**	.365**	1		
	p	.171	.000	.000	.000	.000	.000		1	.005
rminCaH	r	.059	.541**	.494**	.465**	.500**	1			.902
	p	.172	.000	.000	.000	.000		1	.578**	-.076
rmedCaL	r	-.060	.565**	.727**	.739**	1			.000	.079
	p	.162	.000	.000	.000		1	.755**	.701**	-.063
rmaxCaL	r	-.094*	.572**	.670**	1			.000	.000	.142
	p	.029	.000	.000		1	.840**	.728**	.582**	.058
rFBH	r	-.079	.496**	1			.000	.000	.000	-.082
	p	.067	.000		1	.529**	.595**	.587**	.639**	.022
rFBL	r	.018	1			.000	.000	.000	.000	.610
	p	.679		1	.409**	.406**	.469**	.404**	.377**	.012
AGE	r	1			.000	.000	.000	.000	.000	.781
	p		1	.419**	.675**	.583**	.655**	.599**	.724**	.074
				.000	.000	.000	.000	.000	.000	.088
			lmaxCaH	lCaAFH	lminCaH	lmedCaL	lmaxCaL	lFBL	lFBH	AGE

*. Correlation is significant at the 0.05 level (2-tailed), **. Correlation is significant at the 0.01 level (2-tailed), r: right, l: left, FBH: foot bone height, FBL: foot bone length, maxCaL: maximum calcaneus length, medCaL: medial calcaneus length, minCaH: minimum calcaneus height, CaAFH: calcaneus anterior facet height, maxCaH: maximum calcaneus height

In the study, the results of the ROC analysis for the usability of the parameters in gender prediction are presented in tables and graphs (Table 5, Figure 2). Analyzing the data on the right side, the highest accuracy rate was found in right foot bone height (rFBH) (0.913) and rmedCaL (0.910) values. Among the length data, right calcaneus anterior facet height (rCaAFH) (0.737) had the lowest rate of gender prediction accuracy. When the results of the parameters on the left side for gender estimation were analyzed, it was seen that the values on the left side had a higher

accuracy rate in the minCaH and CaAFH parameters, while the data on the right side had a higher accuracy rate in the FBH, FBL, maxCaL, medCaL, maxCaH parameters. Based on the foot model obtained by analyzing all parameters, the parameters on the left side give a reliable rate of 87.5% and the parameters on the right side give a reliable rate of 85.7%. When only the calcaneus data are evaluated, the left side gives a reliable result of 85.2% and the right side 84.9%. Thus, in both models, the left-hand side parameters were found to have a higher accuracy rate.

Table 5. ROC analysis results					
		AUC (95%)	Min-Max	Cut off value	p
Right	FBH	0.841	0.800-0.881	F<84.59<M	0.021*
	FBL	0.913	0.884-0.942	F<247.48<M	<0.001*
	maxCaL	0.904	0.874-0.933	F<83.34<M	<0.001*
	medCaL	0.91	0.883-0.938	F<78.81<M	<0.001*
	minCaH	0.831	0.791-0.87	F<40.53<M	0.020*
	CaAFH	0.737	0.686-0.788	F<26.11<M	0.026*
	maxCaH	0.867	0.832-0.902	F<47.68<M	0.018*
Left	FBH	0.853	0.815-0.892	F<84.50<M	0.020*
	FBL	0.913	0.886-0.94	F<247.63<M	0.014*
	maxCaL	0.897	0.865-0.929	F<84.7<M	0.016*
	medCaL	0.905	0.877-0.933	F<78.36<M	0.014*
	minCaH	0.852	0.816-0.889	F<40.37<M	0.019*
	CaAFH	0.755	0.706-0.803	F<26.13<M	0.025*
	maxCaH	0.852	0.814-0.891	F<47.32<M	0.020*

AUC: area under the ROC curve, Min: minimum value, Max: maximum value, FBH: foot bone height, FBL: foot bone length, maxCaL: maximum calcaneus length, medCaL: medial calcaneus length, minCaH: minimum calcaneus height, CaAFH: calcaneus anterior facet height, maxCaH: maximum calcaneus height, F: female, M: male, p: significance level

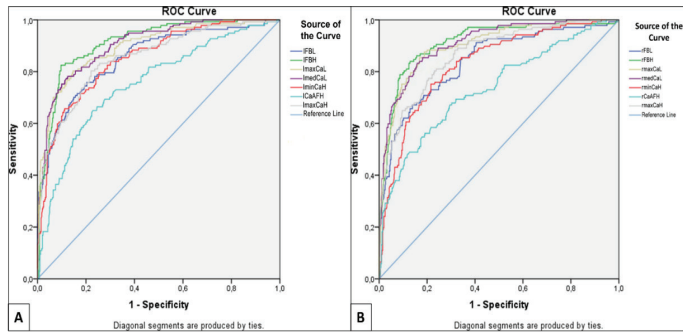


Figure 2. ROC analysis graph for gender prediction (A: Left side, B: Right side)

DISCUSSION

One of the three points of the foot in contact with the ground is the calcaneus. There are studies in the literature on morphometric measurements of both the foot and calcaneus on bones, cadavers, and living specimens (2,4,13,17-21). Evaluation of RI is necessary prior to calcaneus surgical treatment. Furthermore, knowledge of calcaneus morphometry before surgery provides useful information to prevent surgical complications.

Radiological approaches allow the examination of the relevant region without any intervention to the individual during the diagnosis of diseases. The data obtained as a result of radiological measurements of the foot and calcaneus can determine the degree of disease and the programming of treatment in cases involving this area.

Some measurements of the calcaneus are utilized both in clinical practice and in various forensic cases or archaeological excavations to estimate gender from bone (22,23). Distance measurements of the foot and calcaneus were performed within the scope of the study. Considering the biomechanical importance of the calcaneus in the foot, we aimed to determine its relationship with foot bone length and foot bone height. In the literature, there are few studies on RI regarding our measurement parameters in the Turkish population (15,23,24). In the study conducted by Schepers et al. (2007), examining the changes caused by calcaneus fractures in foot measurements in the foot RI of 33 individuals belonging to the Dutch population, the FBH value was 81 mm on the intact side, while this value was 77 mm on the side where the fracture was present, and a statistically significant difference was found between these values. In a study conducted in a German population, the FBH value was 84 mm (25). Altuntas (2021) measured the FBH data on the foot RI of 90 male and 90 female individuals as 84.48 ± 6.12 mm on the right side and 84.5 ± 6 mm on the left side. Altuntas (2021) found a statistical significance between the right and left sides of men in his study ($p=0.022$). However, he reported that there was no statistical significance between the two sides in women (23).

In the present study, no significant difference was found between right and left foot lengths ($p=0.105$). This conclusion supports the results of the study by Zeybek et

al. (2008) on cadavers in which they aimed to estimate gender from foot anthropometric characteristics and Torun and Cay's (2018) study in which they examined the relationship between arcus longitudinalis medialis and foot length bilaterally in 106 patients (19,24). Torun and Cay (2018) reported that the foot dome flattened as the FBL increased. In the study, comparing the FBL values between genders, the lengths of the right and left sides were found to be significantly higher in men ($p<0.001$) (24). This result is consistent with the result obtained by Gwani et al. (2017) who measured foot lengths in two different ways with and without including metatarsal bones (26). Altuntas (2021) reported that the foot lengths of males were significantly higher than females in his study (23). We think that the fact that our measurements in the Turkish population have higher values than the studies of Sanli et al. (2005) and Dogruyol and Cimen (2021) is due to the age difference of the study populations (Table 6). Hill et al. (2017) evaluated the FBL value in their study with the 3D modeling method (27). We think that the differences in this study, which has higher FBL values than the current study, may be due to differences in methodology rather than racial differences in the study population.

There are two measurements of the length of the calcaneus in the study. In the literature, maxCaL is the most evaluated of these lengths, which is generally used in studies to estimate gender. In the study, it was determined that there was no statistically significant difference between the right and left sides of maxCaL data ($p>0.05$). Statistically significant differences were detected in both right and left maxCaL data in males and females ($p<0.001$) (Table 7).

Riepert et al. (1995) found no significant differences between males and females in the sex prediction of calcaneus length in lateral foot RI of 800 individuals from a Central European population ($p<0.001$) (16). Cekdemir et al. (2021) found statistically significant differences between the two sides in their study performed on CT images aiming to predict gender from the calcaneus ($p<0.001$) (28). These results are consistent with the findings of the present study. In addition, there are studies in the literature showing that there are no statistically significant differences between maxCaL lengths on the right and left sides as a result of research on dry bones (2,20). We think that the higher values of the results obtained in the present study compared to studies on cadavers in different populations are due to the different populations. Furthermore, López-Capdevila et al. (2020) measured the maxCaL value as 91 mm before surgical intervention applied to calcaneus fractures and 85.25 mm after surgery (29) (Table 7). They found significant differences between preoperative and postoperative outcomes ($p<0.025$).

We think that the medCaL data obtained in the study is lower than the data obtained by Agoada (2018) due to the difference in sample size and the characteristics of the populations (Table 7) (13).

Table 6. FBL value in other studies in the literature								
Authors	Method	Population	N	Age range	Mean±SD			
Sanlı et al. (2005) (17)	Human	Türkiye	155	17-23	249.10±18.55			
Sen and Ghosh (2008) (18)	Human	India	350	18-50	222.6±1			
Zeybek et al. (2008) (19)	Human	Türkiye	249	18-44	Right		Left	
					Male	Female	Male	Female
					256.01±11.17	230.46±9.03	255.79±11.17	230.79±9.07
Gwani et al. (2017) (26)	RI	Nigeria	32	20-35	Male		Female	
					257.2±11.5		236±10.4	
Hill et al. (2017) (27)	3D Modeling	UK	62	-	Male		Female	
					Right	Left	Right	Left
					268.25±11.52	268.50±12.13	240.22±9.62	240.07±9.76
Torun and Cay (2018) (24)	RI	Türkiye	106	18-80	Male		Female	
					264.1±16.5		237.5±12.1	
Altuntas (2021) (23)	RI	Türkiye	180	20-64	Right		Left	
					261.13±17.28		261.08±17.2	
Dogruyol and Cimen (2021) (15)	RI	Türkiye	662	18-86	Right		Left	
					258.9±22.5		258.1±22.4	
Present study	RI	Türkiye	540	20-65	Right		Left	
					242.04±18.63		242.87±18.08	
					Male	Female	Male	Female
					261.27±16.89	235.5±14.15	261.81±15.13	236.43±14.03

FBL: foot bone length, N: number of individuals, RI: radiography images, 3D: three-dimensional, SD: standard deviation

Table 7. maxCaL and medCaL values in studies in the literature								
maxCaL								
Authors	Method	Population	N	Age range	Mean±SD			
Riepert et al. (1995) (16)	RI	Central Europe	800	20-79	Male		Female	
					89.8±4.7		82±4.6	
Kim et al. (38)	Cadaver	South Korea	42	54-91	74.32±3			
Agoada (2018) (13)	RI and Cadaver	USA	54	35-89	RI		Cadaver	
					86.75±6.72		83.87±6.56	
Amuti et al. (2020) (2)	Cadaver	Kenya	64	18-65	Right		Left	
					68.95±9.85		68.26±10.46	
Schmutz et al. (2020) (4)	3D CT	Thailand and Japan	41	44-90	Right		Left	
					76.31±5.15		76.43±5.26	
Cekdemir et al. (2021) (8)	CT	Türkiye	489	-	Male		Female	
					85.65±5.16		76.74±4.21	
Present study	RI	Türkiye	540	20-65	Right		Left	
					83.12±6.96		83.22±5.96	
					Male	Female	Male	Female
					89.94±5.58	80.81±5.76	89.7±5.6	81.02±4.22
medCaL								
Authors	Method	Population	N	Age range	Mean±SD			
Agoada (2018) (13)	RI and Cadaver	USA	54	35-89	RI		Cadaver	
					83.32±6.74		82.15±6.74	
Altuntas (2021) (23)	RI	Türkiye	180	20-64	Right		Left	
					81.06±6.45		81.02±6.4	
					Male	Female	Male	Female
					85.4±4.9	76.8±4.7	85.3±4.9	76.8±4.7
Present study	RI	Türkiye	540	20-65	Right		Left	
					76.86±6.16		76.79±5.98	
					Male	Female	Male	Female
					83.26±5.29	74.69±4.77	83.02±5.05	74.66±4.64

maxCaL: maximum calcaneus length, medCaL: medial calcaneus length, N: number of individuals, RI: radiographic images, 3D: three-dimensional, CT: computed tomography, SD: standard deviation

There are two different measurements that determine the height of the calcaneus in the study. In the literature, no study has been found in which minCAH and maxCAH measurements were taken the same in the Turkish population. Additionally, in our study, maxCAH and minCAH data were found to have similar accuracy rates in gender prediction. It has been revealed that minCAH measurements can be preferred in bones where maxCAH measurements cannot be taken (Table 5). We think that the differences between the results of Zakaria et al. (2010) and Riepert et al. (1996), whereas the results of the present study and Agoada (2018) are close to each other, are due to the racial characteristics of the populations in the studies (13,16,30) (Table 8).

One of the lengths indicating calcaneus height is maxCaH. In the literature, this value was compared between the sides

with (47 mm) and without (50 mm) calcaneus fracture and it was shown that maxCaH decreased on the fractured side with statistically significant differences ($p=0.001$) (14). Arslan et al. (2014) measured maxCaH as 47.68 ± 2.8 mm in men and 43.16 ± 2.71 mm in women in their study and reported a statistically significant difference between the two sides ($p<0.001$). This result is consistent with the result obtained in the current study ($p<0.001$) (31) (Table 8).

The last length measurement of the calcaneus evaluated in the study was CaAFH. The data obtained by Amuti et al. (2020) have lower values than the data in the present study (2). Cekdemir et al. reported statistically significant differences between the genders in this length in their study in which they aimed to predict gender from the calcaneus ($p<0.001$) (8). These data are consistent with the results of the present study ($p<0.001$) (Table 8).

Table 8. minCaH, maxCaH and CaAFH values in other studies in the literature

minCaH						
Authors	Method	Population	N	Age range	Mean \pm SD	
Riepert et al. (1995) (16)	RI	Central Europe	800	20-79	Male	Female
					42.3 \pm 3.1	37.8 \pm 2.9
Zakaria et al. (2010) (30)	RI	Egypt	204	20-70	Male	Female
					40.29 \pm 3.1	34.59 \pm 3.2
Agoada (2018) (13)	RI and Cadaver	USA	54	35-89	RI	Cadaver
					38.98 \pm 3.82	39.24 \pm 3.65
Present study	RI	Türkiye	540	20-65	Right	Left
					39.57 \pm 4.27	39.43 \pm 4.06
maxCaH						
Riepert et al. (1995) (16)	RI	Central Europe	800	20-79	Male	Female
					51.8 \pm 4.0	46.7 \pm 3.6
Schepers et al. (2007) (14)	RI	Holland	33	18-65	50	
Zakaria et al. (2010) (30)	RI	Egypt	204	20-70	Male	Female
					47.94 \pm 3.5	41.41 \pm 3.5
Arslan et al. (2014) (31)	RI	Türkiye	69	18-79	Male	Female
					47.68 \pm 2.8	43.16 \pm 2.71
Kim et al. (2014) (38)	Cadaver	South Korea	42	54-91	42.5 \pm 3.0	
Agoada (2018) (13)	RI and Cadaver	USA	54	35-89	RI	Cadaver
					50.50 \pm 5.68	49.75 \pm 4.31
Present study	RI	Türkiye	540	20-65	Right	Left
					46.71 \pm 3.93	46.43 \pm 3.75
CaAFH						
Agoada (2018) (13)	RI and Cadaver	USA	54	35-89	RI	Cadaver
					23.08 \pm 2.21	25.07 \pm 2.12
Amuti et al. (2020) (2)	Cadaver	Kenya	64	18-65	Right	Left
					18.83 \pm 4.71	17.91 \pm 3.93
Cekdemir et al. (2021) (28)	CT	Türkiye	489	-	Male	Female
					28.83 \pm 2.13	25.45 \pm 1.99
Present study	RI	Türkiye	540	20-65	Right	Left
					25.73 \pm 2.7	25.76 \pm 3.01

minCaH: minimum calcaneus height, maxCaH: maximum calcaneus height, CaAFH: calcaneus anterior facet height, N: number of individuals, RI: radiographic images, CT: computed tomography, SD: standard deviation

Gender estimation from bones is gaining importance in various forensic cases or major disasters affecting masses (12). Gender estimation from skeletal remains is an important issue in both forensics and bioarchaeology (32). In the present study, right and left calcaneus measurement parameters were subjected to ROC analysis to determine their accuracy in gender prediction. As a result of the analysis, FBL was the parameter with the highest accuracy rate on both the right (0.913) and left (0.913) sides. In the Turkish population, it was reported that the FBL parameter on cadavers (19) and the FBL parameter on RI (23) provided highly accurate results for gender prediction. Fun et al. (2011) reported that the accuracy rate of predicting gender from foot length was 85.7-86.7% in their study in which they stated that predicting gender from foot length has a high accuracy rate (33). Another study reported that FBL is a strong parameter in predicting gender (34). In another study conducted on a northern Australian population, which aimed to predict gender from foot and footprint measurements, it was reported that FBL was 90.5% successful in predicting gender (35). In a study conducted on a Nigerian population that examined the ability to predict gender from foot measurements, height, and body mass index, FBL was found to be an important parameter for gender prediction (36).

In the present study, the accuracy of maxCaL was 0.904 on the right side and 0.897 on the left side. DiMichele and Spradley (2012) reported the accuracy of this parameter in predicting gender as 0.800 (37).

In the study, minCaH had an accuracy of 0.831 on the right side and 0.852 on the left side; CaAFH had an accuracy of 0.737 on the right side and 0.755 on the left side. In the study by Kim et al. (2013) in which these parameters were also evaluated, the accuracy value of maxCaL was 0.902, minCaH value was 0.871 and CaAFH was 0.780 as well (38). In another study, the accuracy of maxCaL was reported to be 83.5%, while the accuracy of CaAFH was 78.7% (39). In a different study, it was reported that maxCaL length was successful by 82.3% in predicting gender. In the same study, the value of minCaH length was reported as 81.2% and CaAFH as 78.5% (10). Ekizoglu et al. (2017) reported that maxCaL was quite different between genders in their study based on computed tomography images (40). Gualdi-Rosso (2007) reported that talus lengths were more successful in predicting gender than calcaneus lengths (22). However, he stated that length and width measurements of the calcaneus were more accurate than height measurements. In another study performed on computed tomography images in the Turkish population, Cekdemir et al. (2021) reported the accuracy of maxCaL as 0.911 and CaAFH as 0.878 (8).

The limitations of our study are that it is a retrospective study and that the individuals participating in the study do not know their body mass index, so the relationship between weight, height and body mass index and our measurement data could not be revealed.

CONCLUSION

The conclusion is very detailed and long written. It will be sufficient to emphasize the result of the study, its difference from other studies and its contribution to the literature in one paragraph.

The calcaneus plays an important role in body biomechanics. One of the most important features that enables it to fulfill this role is that it is one of the strongest bones in the body. Due to its robust structure, the calcaneus can maintain its morphometric properties even under the ground or in natural disasters. In addition to revealing morphometric differences between races, it provides information about people and communities that lived many years ago in forensic medicine, archaeology, and anthropology for gender determination. For these reasons, the morphometric measurements of the calcaneus and the accuracy of these measurements in gender determination were presented in the present study. These data are important for many disciplines such as forensics, archaeology, and anthropology. In this study, we aimed to contribute to the literature with various morphometric measurements of the calcaneus. The study was carried out on 1,080 calcanei belonging to individuals aged 20-65 years. All the values of length were higher in men than in women. Among the parameters in the study, FBL and maxCaL showed the highest accuracy in gender prediction. Besides, the right-side parameters in the study have a higher accuracy rate in gender determination than the left side.

In future studies, the inclusion of individuals under the age of 20 years and over the age of 65 years in studies covering larger populations will allow more comprehensive data on the calcaneus to be obtained. These data can be used for the development of machine learning and artificial intelligence methods in future studies.

It is believed that the results obtained in the study will be helpful in forensic and clinical applications. Knowing the average values of the measured parameters in the Turkish population will allow for more accurate results. Contributory results are presented for situations where gender prediction is required.

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REFERENCES

1. Korkmaz T. Calcaneal and metatarsal weight distribution in children's feet. *Selcuk Med J.* 1989;5:99-106.

2. Amuti T, Muuthuri N, Nichome L, et al. Morphometric dimensions of the calcaneus. *J Foot Ankle Surg.* 2020;59:949-52.
3. Standring S. *Gray's anatomy the anatomical basis of clinical practice.* 42nd edition. Elsevier, Amsterdam, 2020;1347.
4. Schmutz B, Luthi M, Schmutz-Leong YK, et al. Morphological analysis of Gissane's angle utilising a statistical shape model of the calcaneus. *Arch Orthop Trauma Surg.* 2021;141:937-45.
5. Kutlu A. The cavus deformity of the foot and its therapy. *Selcuk Med J.* 1990;6:28-35.
6. Mendonca DS, Kurita LM, Carvalho FSR, et al. Development and validation of a new formula for sex estimation based on multislice computed tomographic measurements of maxillary and frontal sinuses among Brazilian adults. *Dentomaxillofac Radiol.* 2021;50:20200490.
7. Kramer NA, Lopez-Capp TT, Michel-Crosato E, et al. Sex estimation from the mastoid process using Micro-CT among Brazilians: Discriminant analysis and ROC curve analysis. *J Forensic Radiol Imaging.* 2018;14:1-7.
8. Cekdemir YE, Mutlu U, Karaman G, et al. Estimation of sex using morphometric measurements performed on cranial computerized tomography scans. *Radiol Med.* 2021;126:306-15.
9. Garcovich D, Albert Gasco L, Alvarado Lorenzo A, et al. Sex estimation through geometric morphometric analysis of the frontal bone: an assessment in pre-pubertal and post-pubertal modern Spanish population. *Int J Legal Med.* 2022;136:319-28.
10. Zhang K, Fan F, Tu M, et al. Estimation of stature and sex from calcaneal measurements in Chinese. *Aust J Forensic Sci.* 2016;49:69-77.
11. Bidmos MA, Asala SA. Sexual dimorphism of the calcaneus of South African blacks. *J Forensic Sci.* 2004;49:446-50.
12. Scott S, Ruengdit S, Peckmann TR, Mahakkanukrauh P. Sex estimation from measurements of the calcaneus: Applications for personal identification in Thailand. *Forensic Sci Int.* 2018;278:405-e1-8.
13. Agoada D. The relationship between linear osteological and radiographic measurements of the human calcaneus and talus. *Anat Rec.* 2018;301:21-33.
14. Schepers T, Ginai AZ, Mulder PG, et al. Radiographic evaluation of calcaneal fractures: to measure or not to measure. *Skeletal Radiol.* 2007;36:847-52.
15. Dogruyol G, Cimen M. Radiological research of medial and lateral arch angles and foot length in terms of age, gender and side differences. *Turk J Med Sci.* 2021;2:76-83.
16. Riepert T, Drechsler T, Schild H, et al. Estimation of sex on the basis of radiographs of the calcaneus. *Forensic Sci Int.* 1996;77:133-40.
17. Sanlı SG, Kizilkanat ED, Boyan N, et al. Stature estimation based on hand length and foot length. *Clin Anat.* 2005;18:589-96.
18. Sen J, Ghosh S. Estimation of stature from foot length and foot breadth among the Rajbanshi: an indigenous population of North Bengal. *Forensic Sci Int.* 2008;181:55.e1-6.
19. Zeybek G, Ergur I, Demiroglu Z. Stature and gender estimation using foot measurements. *Forensic Sci Int.* 2008;181:54.e1-5.
20. Kim JH, Gwak HJ, Kim JG, et al. Measurement of normal calcaneus in Korean cadavers: a preliminary report. *J Korean foot ankle soc.* 2014;18:14-8.
21. Deniz G, Kaya A, Ercan Z, et al. The evaluation of radiologic angular measurements in patients with foot pain. *J Am Podiatr Med Assoc.* 2020;110:Article_8.
22. Gualdi-Russo E. Sex determination from the talus and calcaneus measurements. *Forensic Sci Int.* 2007;171:151-6.
23. Altuntas E. Sex determination from radiographs of foot bones. Ph.D. thesis, On Dokuz Mayıs University, Samsun, 2021.
24. Torun BI, Cay N. Relationship between the angle of the foot arch and the length of the foot. *Kafkas J Med.* 2018;8:172-7.
25. Rammelt S, Grass R, Zawadski T, et al. Foot function after subtalar distraction bone- block arthrodesis. A prospective study. *J Bone Joint Surg Br.* 2004;86:659-68.
26. Gwani AS, Salihu AT, Garba IS, et al. Estimation of stature from radiographic measurement of foot dimensions: Truncated foot length may be more reliable than full foot length. *J Forensic Leg Med.* 2017;46:53-7.
27. Hill M, Naemi R, Branthwaite H, Chockalingam N. The relationship between arch height and foot length: Implications for size grading. *Appl Ergon.* 2017;59:243-50.
28. Cekdemir YE, Mutlu U, Karaman G, et al. Evaluation of computed tomography images of calcaneus for estimation of sex. *Radiol Med.* 2021;126:1064-73.
29. López-Capdevila L, Santamaria Fumas A, Dominguez Sevilla A, et al. Dorsal wedge calcaneal osteotomy as surgical treatment for insertional Achilles tendinopathy. *Rev Esp Cir Ortop Traumatol (Engl Ed).* 2020; 64:22-7.
30. Zakaria MS, Mohammed AH, Habib SR, et al. Calcaneus radiograph as a diagnostic tool for sexual dimorphism in Egyptians. *J Forensic Leg Med.* 2010;17:378-82.
31. Arslan G, Yirgin IK, Tasguzen A. A measuremental approach to calcaneal fractures. *Eur J Trauma Emerg Surg.* 2014;40:593-9.
32. Gonzalez PN, Bernal V, Perez SI. Geometric morphometric approach to sex estimation of human pelvis. *Forensic Sci Int.* 2009;189:68-74.
33. Fun PS, Osman K, Hamzah SPAA, et al. Stature and sex estimation using foot measurements for Malays and Chinese in Malaysia. *Jurnal Sains Kesihatan Malaysia* 2011;9:23-8.
34. Sen J, Kanchan T, Ghosh S. Sex estimation from foot dimensions in an indigenous Indian population. *J Forensic Sci.* 2011;56:S148-53.
35. Hemy N, Flavel A, Ishak NI, et al. Sex estimation using anthropometry of feet and footprints in a Western Australian population. *Forensic Sci Int.* 2013;231:402.e1-6.
36. Ogbonnaya IO, Frank ET, Olasubomi SA, et al. Sex estimation using foot measurements, stature and body mass index (BMI) in a Nigerian population. *Acta Sci Nat.* 2018;5:32-7.

37. DiMichele DL, Spradley MK. Sex estimation in a modern American osteological sample using a discriminant function analysis from the calcaneus. *Forensic Sci Int.* 2012;221:152.e1-5.
38. Kim DI, Kim YS, Lee UY, Han SH. Sex determination from calcaneus in Korean using discriminant analysis. *Forensic Sci Int.* 2013;228:177.e1-7.
39. Peckmann TR, Orr K, Meek S, Manolis SK. Sex determination from the calcaneus in a 20th century. Greek population using discriminant function analysis. *Sci Justice.* 2015;55:377-82.
40. Ekizoglu O, İnci E, Palabıyık FB, et al. Sex estimation in a contemporary Turkish population based on CT scans of the calcaneus. *Forensic Sci Int.* 2017;279:310.e1-6.



The Relationship Between Pain Intensity, Pain Beliefs, and Emotion Regulation Skills in Non-Surgical Spinal Pathology Pain

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Abstract

Aim: Chronic pain, particularly spinal pain, presents a significant health concern globally. This study aims to investigate the interplay between pain beliefs, emotion regulation strategies, and pain severity in individuals with complaints of spinal pain.

Material and Method: A sample of 100 participants presenting with back and neck pain, without indications for surgery, completed measures assessing pain beliefs, emotion regulation strategies, and pain severity.

Results: Results indicated that individuals with higher levels of psychological pain beliefs reported lower pain severity, while those employing maladaptive emotion regulation strategies experienced greater pain severity.

Conclusion: These findings underscore the importance of considering psychological factors in pain management and highlight the potential utility of targeting emotion regulation strategies in clinical interventions. Future research should further explore the impact of pain beliefs and emotion regulation on treatment outcomes and the pain experience, providing valuable insights for enhancing pain management approaches.

Keywords: Spinal pain, pain beliefs, emotion regulation, spinal pathology

INTRODUCTION

Globally, pain is acknowledged as a common and rising health concern (1). Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (2) by the International Association for the Study of Pain (IASP). Individuals perceive body sensations and somatic complaints differently, and research supports the idea that people perceive pain differently (3).

Research involving individuals with chronic pain has demonstrated that anxiety and depressive symptoms frequently coexist with the pain (4). Moreover, it has been shown that depressed symptoms are linked to elevated pain-related disability, catastrophic thinking, and functional impairment in these persons (5). Furthermore, studies suggest that a number of variables, including age, a sedentary lifestyle, low or inadequate levels of 25 (OH) vitamin D, obesity, and smoking, may contribute to the genesis of chronic neck and back pain (6,7). Furthermore,

it has been proposed that psychological variables like anxiety and depression may account for variations in treatment response within a subgroup of patients, even in the face of multiple medical and surgical treatment methods for patients with chronic back and neck pain (8).

Studies have shown that chronic pain is more common in people with premorbid psychosocial stresses such as depression or anxiety (9). This phenomenon can be explained by the theory that psychosocial elements become more prominent when pain becomes persistent, creating a vicious cycle that intensifies the person's pain experience and degree of impairment. Thus, in order to establish a thorough understanding and useful intervention techniques, addressing pain from a biopsychosocial viewpoint requires taking into account not only physical variables but also the patient's psychological and social surroundings (10). Accordingly, pain is a multifaceted phenomenon that has elements related to neurophysiology, biochemistry, psychology, ethnicity, culture, cognition, and environment (11).

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Research examining pain from a biopsychosocial standpoint has demonstrated that a patient's expectations, beliefs, coping strategies, social support, diagnoses, health insurance, and even the employer's response can all affect how well they manage their pain (12). Of them, the idea of pain beliefs is particularly noteworthy.

According to Ellis, pain beliefs are made up of cognitions, thoughts, attitudes, and emotions. Research on pain beliefs has also shown that people who stop their treatment tend to have more negative pain beliefs. However, it is anticipated that these beliefs will lessen with cognitive-behavioral therapy (13). "Patients' beliefs about the causes of their pain and the expected effects of treatment" (14) is the definition of pain belief. Two sub-dimensions comprised organic pain beliefs that signal physical pain and pose a threat to well-being and psychological pain beliefs that involve interior consequences and emotions impacting the pain experience (15). While certain beliefs may help people cope with their pain (16), negative views about pain have been linked to higher use of healthcare resources and the use of analgesic medications (17), as well as being predictive of pain severity, disability, and distress (18).

It has also been noted that disruption in emotion regulation influences pain beliefs as well as the sensation of pain. Ellis points out that emotion regulation dysfunction is characterized by a lack of awareness of one's emotions, an inability to accept emotions, and an inability to manage behaviors in reaction to negative emotions (19). Pain beliefs, on the other hand, contain cognitions, thoughts, attitudes, and emotions (13). Since unfavorable life events have been shown to disrupt emotion regulation abilities and emotion regulation dysfunction is linked to somatization, it is crucial to comprehend how emotion regulation dysfunction affects the pain experience in this instance (20). Dysfunction in emotion regulation can make it difficult to accurately measure the level of pain and other factors associated with pain, which can make evaluation challenging (21,22). Research has indicated that people who struggle with controlling their emotions are more prone to abuse opioids for pain relief, which increases the intensity of pain and feeds a vicious cycle by impairing positive emotion regulation (23). In this context, it has been suggested that emotion regulation techniques may be helpful in the treatment of pain, underscoring the need for more research in this field (24).

Our study aims to evaluate the concurrent testing of pain-related beliefs and emotion regulation skills in individuals with complaints of spinal pain, given the 75-85% lifetime prevalence of spinal pain (25). Considering the lack of research in this field, we aim to thoroughly assess the connection between pain-related beliefs, emotion regulation abilities, and pain severity.

MATERIAL AND METHOD

Informed consent forms were signed by 100 participants who did not require surgery but came to the Brain and

Neurosurgery Clinic of Karabük University Training and Research Hospital between June 2022 and August 2022 with complaints of pain related to spinal pathologies. The participants ranged in age from 18 to 65, were literate in Turkish, and had no history of medication usage that could have led to mental symptoms or cognitive impairment. Additionally, they had no additional neurological, chronic medical, or psychiatric illnesses that could affect cognitive performance. They also did not have any other rheumatologic conditions.

Those who accepted to participate and fulfilled the inclusion criteria were given a sociodemographic information form created by our team as part of the study. In addition, the participants' own Pain Beliefs Questionnaire, Cognitive Emotion Regulation Questionnaire, and The Short-Form McGill Pain Questionnaire were given out. The Karabük University Non-Interventional Clinical Research Ethics Committee examined and authorized our investigation; the approval number for the study is 2022/924, dated May 31, 2022. The Helsinki Declaration's guiding principles were followed in the conducting of the study.

Measures

Sociodemographic data form: Developed by researchers, this form asks descriptive questions about the participant's gender, age, place of birth, educational background, and, if they are a student, their academic year as well as whether they have ever had a mental health diagnosis.

Pain Beliefs Questionnaire (PBQ): The Pain Beliefs Questionnaire (PBQ), created by Edwards et al. in 1992, has two subscales: the four-item Psychological Beliefs subscale and the eight-item Organic Beliefs subscale. Understanding the psychological and biological attributions of patients with chronic pain—which had not been previously investigated—was the primary goal of establishing the scale. The following are the item numbers for each subscale:

Items 1, 2, 3, 5, 7, 8, 10, and 11 are examples of organic beliefs. Beliefs in psychology: Items 4, 6, 9, 12. Participants are asked to check the option from six possibilities, numbered from 1. "never" to 6. "always," that best describes them. For every item, scores range from 1 to 6. The sum of the scores from all of the items in a subscale divided by the total number of items in that subscale yields the overall score for each subscale (26). Sertel-Berk (27) conducted the validity and reliability assessment for the Turkish version.

The Short-Form McGill Pain Questionnaire (SF-MPQ): A popular tool for measuring pain is the Short-Form McGill Pain Questionnaire (SF-MPQ), which was created by Melzack in 1987 and has been tested for validity and reliability in Turkish. The sensory (11 words) and affective (4 words) components of pain are assessed using a total of 15 descriptive words in this questionnaire. The three pain scores that result from this component of the

questionnaire are sensory, affective, and total pain ratio (sensory+affective), where 0 represents no pain, 1 is mild, 2 is moderate, and three is severe. A 6-point Likert scale is used to quantify overall pain severity, and a Visual Analog Scale (VAS) is used to assess pain felt at the time of assessment. 0 on this scale indicates no pain, one mild pain, two upsetting pain, three bothersome pain, four terrible pain, and five agonizing pain (28,29).

The Cognitive Emotion Regulation Questionnaire (CERQ): Garnefski, Kraaij, and Spinhoven (30) created the Cognitive Emotion Regulation Questionnaire (CERQ), a five-point Likert-type assessment tool (1=not at all suited for me, 2=slightly suitable for me, 3=partially suitable for me, 4=extremely suitable for me, and 5=totally suitable for me). There are 36 items in all on the scale. The Cronbach's alpha coefficient in the scale's initial iteration spans from.67 to.81. Self-blame, acceptance, centering on planning, positive refocusing, positive reappraisal, putting into perspective, catastrophizing, other-blame, and rumination are the nine subscales that make up the scale. Onat and Otrar (31) carried out the scale's adaption into Turkish and validity and reliability investigations. The results showed a test-retest reliability coefficient of $r=.1,00$ and a Cronbach's alpha value of $\alpha=.784$. The validity studies employed the criterion-related validity technique. The Negative Affect Scale and the Cognitive Emotion Regulation Questionnaire were shown to be statistically significantly correlated ($r=-.572$).

Statistical Analysis

IBM SPSS 21 software was used for statistical analysis. Normality distribution was checked using the Shapiro-Wilk test. Normally distributed data were presented as mean±standard deviation, while data that did not show normal distribution were presented as median (min-max). Chi-square test was used for comparing genders between groups. For comparing numerical variables between groups, T-test was used when data were normally distributed, and Mann-Whitney U test was used when at least one data did not follow normal distribution. The relationship between variables was evaluated using the Spearman correlation test. The significance level was set at 0.05.

RESULTS

A total of 100 patients presenting with complaints of back and neck pain to the Brain Surgery Polyclinic of Karabuk Education and Research Hospital, who were examined by a neurosurgeon and found to have no pathologies requiring surgery, were included in our study.

Since cutoff scores for the scales we used were not available and to ensure standardization, we categorized the SF-MPQ Pain Severity Scale based on mean values. Accordingly, in our statistical analysis, we classified individuals with SF-MPQ Pain Severity Scale scores below 17 as having low-level pain, and those with scores above 17 as having high-level pain. Demographic and clinical data according to this classification are presented in Table 1.

Table 1. Demographic and clinical data according to McGill Pain Questionnaire severity

	Low McGill score n: 48	High McGill score n: 52	P
Gender			0.488 ^a
Woman	35	41	
Man	13	11	
Age	45.31±11.57	41.63±11.39	0.232 ^c
Occupation			0.62 ^a
Unemployed	4	13	
Employed	18	11	
Retired	3	6	
Housewife	23	22	
Educational level			0.292 ^a
Primary school	20	31	
High school	11	10	
Associate degree	6	5	
Bachelor's degree	11	6	
Pain beliefs			
Organic beliefs	26.04±6.27	24.15±6.15	0.132 ^b
Psychological beliefs	9 (4-24)	6 (4-17)	0.002^c
Cognitive emotion regulation			
Self-blame	11 (4-20)	15.5 (4-20)	0.022^c
Acceptance	12.50±3.88	15 (4-20)	0.018^c
Thought focus - deep thinking	10 (5-20)	13.75±4.19	0.004^c
Positive refocusing	11.54±4.60	14 (4-20)	0.016^c
Re-focusing on planning	16 (5-20)	18 (9-20)	0.087 ^c
Positive reappraisal	16 (8-20)	18 (6-20)	0.132 ^c
Reframing	16 (8-20)	18 (6-20)	0.005^c
Ruin	8 (4-20)	8.50 (4-20)	0.151 ^c
Blaming others	6 (4-18)	9 (4-20)	0.013^c

a: Chi-Square test, b: t test, c: Mann Whitney U test

In our study, 76 female and 24 male patients participated, and there was no difference between the two sexes in terms of pain severity. The mean age of the participants was 43.4±11.57 years. There were no significant differences in age, occupation, or educational status among the participants.

Of the participants, 51% were primary school graduates, 75% were married, and 29% were employed.

It was found that individuals with higher levels of psychological pain beliefs experienced significantly lower pain severity ($p=0.022$). Similarly, individuals who used cognitive emotion regulation strategies such as self-blame ($p=0.022$), acceptance ($p=0.018$), refocusing on planning ($p=0.004$), positive refocusing ($p=0.016$), putting into

perspective ($p=0.005$), and other-blame ($p=0.013$) were found to experience statistically more severe pain.

Furthermore, the relationship between pain beliefs and emotion regulation strategies with pain was evaluated in our study, and the data are presented in Table 2.

Table 2: Relationship between McGill Pain Questionnaire and Pain Beliefs and CERS Subscales		
	Mcgill Pain Mean \pm sd	
	Meas \pm sd	Correlation coefficient (r)/ p*
	17.31 \pm 9.01	
Organic beliefs	25.06 \pm 6.25	-0.19/0.051
Psychological beliefs	9.00 \pm 4.58	-0.26/0.007
Self-blame	12.90 \pm 4.90	0.25/0.012
Acceptance	13.41 \pm 3.99	0.23/0.017
Thought focus - deep thinking	12.58 \pm 4.51	0.29/0.003
Positive refocusing	12.69 \pm 4.57	0.16/0.093
Re-focusing on planning	16.17 \pm 3.50	0.17/0.083
Positive reappraisal	15.84 \pm 3.71	0.19/0.051
Reframing	16.02 \pm 3.52	0.32/0.001
Ruin	9.15 \pm 4.53	0.18/0.060
Blaming others	8.90 \pm 4.81	0.24/0.013
Spearman correlation test		

According to the statistical evaluation, individuals who perceive lower pain severity tend to have higher levels of psychological pain beliefs. Additionally, the use of cognitive emotion regulation strategies such as self-blame, acceptance, refocusing on planning, putting into perspective, and other-blame is associated with increased pain severity. However, no significant relationship was found between subgroups of organic beliefs, psychological beliefs, and emotion regulation skills.

DISCUSSION

Numerous elements, including those that are structural, physical, psychological, social, lifestyle, and related health factors that interact, might affect the condition of pain. As such, it is critical to address pain from a biopsychosocial perspective (32,33). People who experience pain not only bear a physical burden but also financial difficulties, which are exacerbated by psychological considerations (34). Body language serves as a means of expressing psychological conflicts, anxieties, and wants when accompanied by psychological elements. There are variations in the degree of pain and how it is treated due to this vicious cycle, which also has an impact on people's mental and social circumstances (35).

It has been proposed that disparities in coping mechanisms for addressing pain may result from views about the biological or psychological causes of pain (36).

The majority of participants in our survey believed that pain results from physical damage, and we were unable to discover a meaningful correlation between the severity of pain and organic pain beliefs. Nonetheless, people with more prevalent psychological pain beliefs reported less severe pain, which is in line with the literature. Those without any health problems had higher psychological pain beliefs, according to Edwards et al. (1992) (26). Like our investigation, Ulus et al. (2014) discovered that people with less severe pain reported more common psychological pain beliefs (37). As evidenced by the findings of the Edwards et al. study, those without a history of suffering may express their discomfort less severely, given that attitudes about pain are particularly influenced by past experiences or lessons (38). This condition in our study may have resulted from those with low-level spinal pain not contemplating any damage to the affected area because they did not see the reason of their pain as physical. To clarify this part of pain sensation that has remained unclear, more research is required. Research has demonstrated that psychological factors are linked to different elements of pain, including chronicity and treatment resistance, which can affect functioning (39). We also looked at the connection, as shown in recent research (20), between emotion management techniques—specifically, somatization—and pain. Research on the relationship between pain and emotion regulation is scarce, but what is known is that those who use improper emotion regulation techniques typically have more severe pain (40). In line with these conclusions, our research also found that people who engage in unhealthy emotion regulation techniques—specifically, self-blame, rumination/deep thinking, and blaming others—tend to experience pain more acutely. In this sense, our work is consistent with the corpus of prior studies. It's common knowledge that those who have trouble controlling their emotions frequently somatize their feelings. When our participants employ improper emotion regulation techniques and give their current discomfort greater relevance, they may feel it more keenly.

The cognitive states that are absent from the literature are those that are still not well known in regard to this field. Thus, more investigation is required to comprehend the reactions to pain. Although the majority of the literature is supported by our findings, it is important to emphasize that those who use appropriate emotion regulation techniques—like acceptance and perspective—also report higher degrees of pain severity. While there isn't any information about this problem in the literature, it's hypothesized that this might be caused by the fact that there isn't a single cause for pain. Even while some people manage their emotions appropriately, there could be other factors that influence how intense pain feels to them. It is crucial to take into account how and when people employ emotion regulation techniques, as well as how this influences the management and treatment of pain. Therefore, the emphasis should be on comprehending how patients apply emotion regulation techniques and how those strategies affect pain management and persistence.

In the literature, no study investigating the relationship between pain beliefs and emotion regulation strategies in pain severity has been found. Our study is considered important in supporting the multidimensional investigation of psychiatric parameters in the etiology, progression, and resolution of pain. The fact that our study was conducted face-to-face with patients is also one of our strengths. However, our study has limitations, such as the lack of examination of how these parameters affect pain and their relationship with the treatment process. Additionally, our evaluation of spinal pain as a general concept in our study may have affected its standardization. In future studies, evaluating specific pathologies related to spinal pain, investigating the effects of pain beliefs and emotion regulation strategies on the process and treatment, and assessing the effectiveness of therapy would be beneficial.

CONCLUSION

Our study examined the relationship between pain severity and psychological parameters such as pain beliefs and emotion regulation strategies. In this context, individuals who endorsed higher levels of psychological pain beliefs reported lower levels of pain, while those who employed inappropriate emotion regulation strategies experienced more severe pain. Future research investigating the effects of pain beliefs and emotion regulation strategies on the pain process and treatment may provide valuable insights for clinical practice and the development of pain management strategies.

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Ethical approval: *The Karabük University Non-Interventional Clinical Research Ethics Committee examined and authorized our investigation; the approval number for the study is 2022/924, dated May 31, 2022. The Helsinki Declaration's guiding principles were followed in the conducting of the study.*

REFERENCES

- Kuru T, Yeldan İ, Zengin A, et al. The prevalence of pain and different pain treatments in adults. *AGRI*. 2011;23:22-7.
- Merskey H, Bogduk N. Classification of chronic pain. 2nd Edition, IASP Task Force on Taxonomy. IASP Press, Seattle. 1994;209-14.
- Eisenberg L. What makes persons "patients" and patients "well? *Am J Med*. 1980;69:277-86.
- Reed BD, Haefner HK, Punch MR, et al. Psychosocial and sexual functioning in women with vulvodynia and chronic pelvic pain. A comparative evaluation. *J Reprod Med*. 2000;45:624-32.
- Bryant C, Cockburn R, Plante AF, Chia A. The psychological profile of women presenting to a multidisciplinary clinic for chronic pelvic pain: high levels of psychological dysfunction and implications for practice. *J Pain Res*. 2016;16:1049-56.
- Jahre H, Grotle M, Smedbråten K, et al. Risk factors for non-specific neck pain in young adults. A systematic review. *BMC Musculoskelet Disord*. 2020;21:366.
- Nieminen LK, Pyysalo LM, Kankaanpää MJ. Prognostic factors for pain chronicity in low back pain: a systematic review. *Pain Rep*. 2021;6:e919.
- Oliveira DS, Vélia Ferreira Mendonça L, Sofia Monteiro Sampaio R, et al. The impact of anxiety and depression on the outcomes of chronic low back pain multidisciplinary pain management-a multicenter prospective cohort study in pain clinics with one-year follow-up. *Pain Med*. 2019;20:736-46.
- Hallegraeff JM, Kan R, van Trijffel E, et al. State anxiety improves prediction of pain and pain-related disability after 12 weeks in patients with acute low back pain: a cohort study. *J Physiother*. 2020;66:39-44.
- Turk DC, Okifuji A. Psychological factors in chronic pain: evolution and revolution. *J Consult Clin Psychol*. 2002;70:678-90.
- Çeliker R. Chronic Pain Syndromes. *Turk J Phys Med Rehab*. 2005;51:B14-8.
- Peker Salt D. Ağrı yakınması olan hastalarda yaşam kalitesi, başa çıkma tutumları ve depresif belirtilerin ağrı algısı ile ilişkisi. Master thesis, Adnan Menderes University, Aydın, 2007.
- Rainville J, Ahern DK, Phalen L. Altering beliefs about pain and impairment in a functionally oriented treatment program for chronic low back pain. *Clin J Pain*. 1993;9:196-201.
- Walsh DA, Radcliffe JC. Pain beliefs and perceived physical disability of patients with chronic low back pain. *Pain*. 2002;97:23-31.
- Yildizeli Topcu S. Relations among pain, pain beliefs, and psychological well-being in patients with chronic pain. *Pain Manag Nurs*. 2018;19:637-44.
- Jensen MP, Turner JA, Romano JM, Lawler BK. Relationship of pain-specific beliefs to chronic pain adjustment. *Pain*. 1994;57:301-9.
- Gil KM, Abrams MR, Phillips G, Keefe FJ. Sickle cell disease pain: the relation of coping strategies to adjustment. *J Consult Clin Psych*. 1989;57:725-31.
- Boothby JL, Thorn BE, Stoud MW, Jensen MP. Coping with chronic pain. In: Gatchel RJ, Turk DJ, eds. *Psychosocial factors in pain: critical perspectives*, New York: Guilford publications, 1999;343-59.
- Svaldi J, Griepenstroh J, Tuschen-Caffier B, Ehring T. Emotion regulation deficits in eating disorders: a marker of eating pathology or general psychopathology?. *Psychiatry Res*. 2012;197:103-11.
- Chalk R, Gibbons A, Scarupa HJ. The multiple dimensions of child abuse and neglect: new insights into an old problem. *Child Trends Research Brief*. 2002. Doi: 10.1037/e479342006-001
- Ehring T, Tuschen-Caffier B, Schnülle J, et al. Emotion regulation and vulnerability to depression: spontaneous versus instructed use of emotion suppression and reappraisal. *Emotion*. 2010;10:563-72.

22. Naragon-Gainey K. Meta-analysis of the relations of anxiety sensitivity to the depressive and anxiety disorders. *Psychol Bull.* 2010;136:128-50.
23. Riquino MR, Priddy SE, Howard MO, Garland EL. Emotion dysregulation as a transdiagnostic mechanism of opioid misuse and suicidality among chronic pain patients. *Borderline Personal Disord Emot Dysregul.* 2018;5:11.
24. Koechlin H, Coakley R, Schechter N, et al. The role of emotion regulation in chronic pain: a systematic literature review. *J Psychosom Res.* 2018;107:38-45.
25. Vialle LR, Wang JC, Lamartina C. *AOSpine Masters Series: Back Pain.* 8th edition. Thieme medical publishers Inc., New York, 2017.
26. Edwards LC, Pearce SA, Turner-Stokes L, Jones A. The Pain Beliefs Questionnaire: an investigation of beliefs in the causes and consequences of pain. *Pain.* 1992;51:267-72.
27. Sertel Berk HÖ. The experience of chronic pain and pain beliefs: The Turkish validation study of the pain beliefs questionnaire. Ph.D thesis, İstanbul University, İstanbul, 2006.
28. Melzack R. The short-form McGill Pain Questionnaire. *Pain.* 1987;30:191-7.
29. Yakut Y, Yakut E, Bayar K, Uygur F. Reliability and validity of the Turkish version short-form McGill pain questionnaire in patients with rheumatoid arthritis. *Clin Rheumatol.* 2007;26:1083-7.
30. Garnefski N, Kraaij V. The cognitive emotion regulation questionnaire. *European Journal of Psychological Assessment.* 2007;23:141-9.
31. Onat O, Otrar M. Adaptation of Cognitive Emotion Regulation Questionnaire to Turkish: validity and reliability studies. *M.Ü. Atatürk Eğitim Fakültesi Eğitim Bilimleri Dergisi.* 2010;31:123-43.
32. Kittelson AJ, George SZ, Maluf KS, Stevens-Lapsley JE. Future directions in painful knee osteoarthritis: harnessing complexity in a heterogeneous population. *Phys Ther.* 2014;94:422-32.
33. Lin I, Wiles L, Waller R, et al. What does best practice care for musculoskeletal pain look like? Eleven consistent recommendations from high-quality clinical practice guidelines: systematic review. *Br J Sports Med.* 2020;54:79-86.
34. Hartvigsen J, Hancock MJ, Kongsted A, et al.; Lancet Low Back Pain Series Working Group. What low back pain is and why we need to pay attention. *Lancet.* 2018;391:2356-67.
35. Kırpınar İ. Ağrı ve depresyon. In: Bekaroğlu M, ed, *Depresyon III. Anadolu psikiyatri günleri*, 1st edition, Karadeniz Ruhsağlığı Yayınları, Trabzon, 1995: 231-9.
36. Öztürk Birge A, Mollaoğlu M. Pain beliefs of patients and the nonpharmacological methods they use to manage the pain. *Agri.* 2018;30:84-92.
37. Ulus B, Irban A, Bakırcı N, et al. Determination of pain characteristics, pain belief and risk of depression among elderly residents living at nursing home. *Turk Geriatri Dergisi* 2014;17:180-7.
38. Gravani S, Matiatou M, Nikolaidis PT, et al. Anxiety and depression affect early postoperative pain dimensions after bariatric surgery. *J Clin Med.* 2020;10:53.
39. Leeuw M, Goossens ME, Linton SJ, et al. The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. *J Behav Med.* 2007;30:77-94.
40. Ruiz-Aranda D, Salguero JM, Fernández-Berrocal P. Emotional regulation and acute pain perception in women. *J Pain.* 2010;11:564-9.



Design of an Insulin Tracer Protein-Based Biosensor for Insulin Determination

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Abstract

Aim: The regulation of blood glucose levels is controlled by insulin, which is produced by the pancreatic beta system. Inadequate synthesis of beta insulin, results in elevated glucose levels, a condition known as diabetes, which can lead to various chronic health issues. In recent times, the diagnosis of diabetes, particularly type 1, has shifted towards the direct measurement of insulin levels. To facilitate this, an immunosensor was created to enable rapid and sensitive examination of insulin levels, with the goal of improving the quality of life for diabetic patients.

Material and Method: For this purpose, an insulin tracer protein based biosensor was designed for the determination of insulin at all solutions. For determination of insulin, electrobiochemical analyses were performed. Optimisation and characterisation studies were performed using differential pulse voltammetry. The performance of bioelectrochemical system was analysed by Receiver Operating Characteristic method.

Results: The insulin biosensor cyclic voltammogram was obtained between -0,1 and 0,6 V potential. At 0,45 V was found as the anodic peak side for determination the insulin. Optimisation and characterisation studies performed at 0,45 V with differential pulse voltammetry.

Conclusion: The study successfully identified stable and easy-to-use insulin concentrations, indicating the potential of the newly developed immunosensor for applications in clinical biochemistry laboratories.

Keywords: Insulin tracer protein, biosensor, insulin

INTRODUCTION

Insulin is secreted by the beta system of the pancreas to take part in blood glucose level regulation when the plasma glucose level increases (1). An increase in blood glucose levels due to the inability to synthesize sufficient beta insulin is known as diabetes and is seen a cause of chronic kidney disease, cardiological disease and blindness in humans (2). The clinical diagnosis of diabetes is type 1 and type 2, mainly due to transmission (3). While the hyperglycaemic picture seen due to insulin not being synthesised as a result of beta damage marks type 1, decreased insulin secretion or tissue resistance to insulin causes permanent type 2 (4,5). In the early stages of type 2, insulin synthesis increases to regulate the plasma glucose level, but insulin resistance is prevented. The flow of time in the beta system cannot be maintained and hyperglycemia develops. 90% of diabetes cases worldwide are type 2 (3).

Those with suspected diabetes or insulin irregularity may face hyperglycemia and related diabetes complications for a long time before diagnosis. Diabetes and the amount it causes can be kept under control by regularly monitoring the amount of insulin (2). For years, they have been trying to protect themselves from the consequences of diabetes by monitoring blood sugar levels using glucose biosensors. However, insulin is an alternative method for controlling blood glucose levels in patients with diabetes, and insulin obtained as a result of incorrectly evaluated glucose levels can cause serious hypoglycemic or hyperglycemic conditions. This will provide a healthier approach for devices that directly monitor diabetes by measuring insulin rather than glucose (6). Biosensor devices have recently taken their place in new studies for use in laboratory examinations due to their high sensitivity, short-time results and low cost advantages. Various studies have attempted to develop insulin detection devices, but insufficient

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sensitivity, difficulty in detecting in the correct range, and stability problems have caused problems in measurement techniques. Laboratory tests used for insulin detection are time-consuming and require expensive equipment and experienced personnel (6).

Glucose monitoring plays a crucial role in the initial diagnosis and ongoing management of diabetes mellitus. However, alongside monitoring glucose levels, keeping track of insulin levels is equally essential as it offers valuable insights into the progression and control of the condition. Therefore, the monitoring of insulin levels holds significant medical significance in the management of diabetes (2,6).

The electrobiochemical method for insulin determination presents novel perspectives for laboratory diagnosis in contrast to conventional approaches. While traditional methods rely on specialized and costly medical equipment, bioelectrochemistry provides the advantage of affordable and portable devices (3). The insulin biosensor investigated in our study holds promise as a model for the development of user-friendly and convenient portable/wearable medical devices.

Therefore, in our study, an immunosensor was developed to perform rapid and sensitive examination of insulin levels to ensure regular insulin monitoring in order to maintain the quality of life of diabetic patients. With the developed immunosensor, shelf-stable and easy-to-use insulin concentrations can be detected.

MATERIAL AND METHOD

Chemicals

All biochemical solutions were freshly prepared before the experiment. The source of all the chemicals acquired was SPI bio Inc, a company situated in France. The experiment involved the utilisation of various solution concentrations to identify the most favourable working conditions and to select the optimal potential differences for further investigation. For determining insulin, insulin tracer protein was used. Stock insulin (5×10^{-3} M) was diluted 100-fold.

No biological samples from humans or animals were used in the studies. All solutions used are commercially available products. For this reason, ethics committee approval is not required in this study.

Apparatus

In order to conduct the electrobiochemical measurements, the experimental setup involved the utilisation of a gold working electrode, which was paired with the Ag/AgCl reference electrode and the Au/Pd auxiliary electrode. The electrochemical potential was measured using an Ivium potentiostat (Netherlands).

Statistical Analysis

Statistical analysis performed by SPSS 20 program.

Biosensor System Preparation

Before the formation of the bioactive layer, the gold working electrode surface underwent polishing using alumina slurries on microfiber to achieve a pristine surface. The pristine gold working electrode was then washed twice with distilled water to eliminate any remnants of the alumina slurries. Subsequently, the electrode was sonicated in pure ethanol to eliminate any undispersed absorbable particles and was washed twice with distilled water (7). Moving on to the next stage, for the immobilisation of the insulin tracer protein, the gold electrode was initially coated with BSA and gelatine through a self-assembled monolayer (SAM) (8). The Au electrode was then paired with the Ag/AgCl as reference electrode. During the electrode preparation for insulin determination, insulin tracer protein was immobilised on a pre-made Au electrode. To achieve this, 250 μ l of insulin tracer protein was deposited in an Eppendorf tube.

RESULTS

Immobilisation

The research conducted demonstrated that through the utilisation of SAM in the immobilisation process, a durable bioactive film was established on the substrate, effectively inhibiting the detachment of bioreceptors from the surface. Consequently, this approach led to enhanced stability during prolonged utilisation of the insulin tracer protein.

Electrochemical Characterisation of the Insulin Biosensor

Insulin biosensors were employed to analyse the electrochemical properties of biosensors through the use of cyclic voltammetry. Cyclic voltammograms were employed to identify the potential point of 0.45 V in the study. The biosensor working range cycle voltammogram is shown as Figure 1.

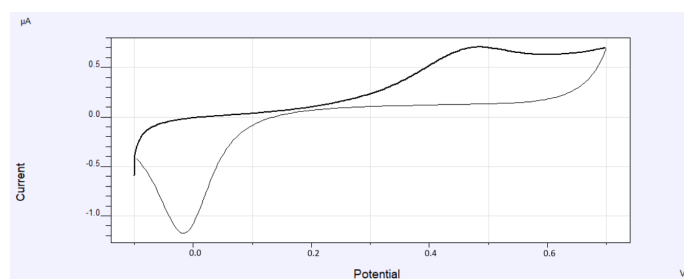


Figure 1. Biosensors cyclic voltammogram (phosphate buffer solution at a 0.3 Vs⁻¹ scan rate)

Optimisation of the Bioactive Layer of the Biosensor

Biologically active films play a crucial role in the operation of biosensors by serving as a medium for detecting and quantifying analytes (9). These layers facilitate the identification and specificity of particular analytes. To enhance the performance of the bioactive layer in biosensors, the impact of insulin tracer protein concentration and polymerisation time on the electrochemical measurement was examined (10). The differential pulse voltammetry curve of the optimised biosensor is shown in Figure 2.

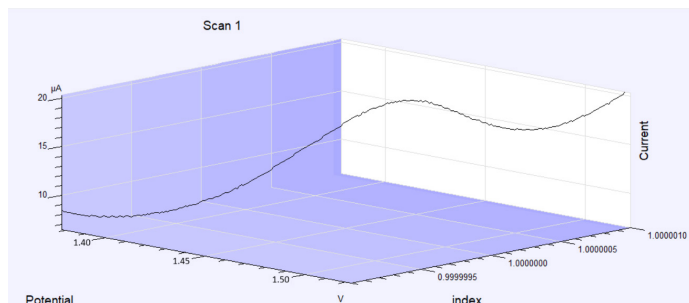


Figure 2. Differential pulse voltammetry of insulin biosensor

Effect of Insulin Tracer Protein Concentration

The concentration of the insulin tracer protein plays a crucial role in determining the sensitivity of the biosensor, as the potentiometric responses of the biosensor rely on the insulin tracer protein's activity (11,12).

In order to investigate the insulin tracer protein's impact on the biosensor's response, various concentrations of the insulin tracer protein (0.05, 0.1, 0.2, 0.4, and 0.6 mg/mL) were utilised.

The experimental findings revealed that a well-defined calibration curve was achieved when the bioactive layer of the biosensor contained 0.2 mg/mL of insulin tracer protein shown as Figure 3.

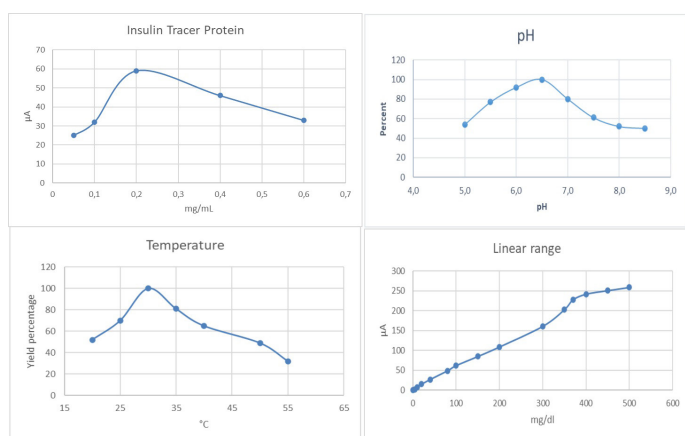


Figure 3. Optimisation and characterisation of insulin biosensor

Biosensor Working Condition Optimisation

pH effect on the biosensor response

The achievement of optimal responses from insulin tracer proteins depends on the presence of a suitable pH medium (13). In order to assess the impact of pH on the biosensor response, various buffers were employed at different pH levels. These buffers consisted of acetate (pH 5.0–5.5) at a concentration of 50 mM, phosphate (pH 6.0–6.5–7.0–7.5), and Tris-HCl (pH 8.0–8.5). The most favorable pH value, determined by a 100% activity rate, was 6.5. Deviations from this optimal pH value, either above or below, resulted in a decline in the biosensor response, as depicted in Figure 3.

According to existing literature, the appropriate pH range for insulin tracer protein is between 6.5 and 7.5. Figure 4 demonstrates that an increase in pH beyond 6.5 reduces in signal intensity due to a loss of insulin tracer protein

activity. The structure of is characterized by the presence of three disulphide bridges, which play a crucial role in maintaining the insulin tracer protein's stability and activity. pH values exceeding 6.5 can disrupt the protein structure, causing alterations in the protein structure and subsequent activity loss. Under acidic conditions, the protonation of amino acids may result in a positive charge, thereby influencing the protein's activity through modifications in the electrostatic interactions among charged residues within the insulin tracer protein's active site. Furthermore, a pH under 6.5 inhibits the function.

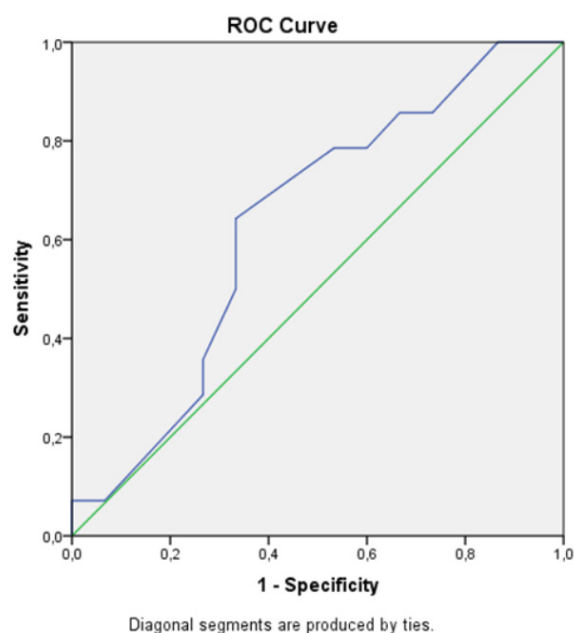


Figure 4. Insulin biosensors ROC curve

Temperature effect

The investigation aimed to assess the impact of temperature on the response of the biosensor (14), thus, a range of temperatures (20–55°C) was analysed. The optimal working temperature for the biosensors was 30°C. Notably, the biosensor response exhibited a direct correlation with temperature up to 30°C, after which any subsequent rise in temperature resulted in a decline in the biosensor response (Figure 3).

Electrochemical Analyses Analytical Characteristics

Range of linear detection

The term "linear detection range" pertains to the range of values within which a biosensor is capable of measuring (15). In this study, a linear calibration curve was established by measuring concentrations of insulin ranging from 10 to 370 mg/dL under the most favourable experimental conditions. The quantification and detection limits were determined on the basis of well-defined calibration curves for an insulin concentration of 50 mg/dl, with a sample size of 10 (Figure 3).

Repeatability and Reproducibility

Repeatability refers to the degree of consistency in the detection outcomes of a particular technic within a short

time frame (16). In the case of the biosensor repeatability experiments, the concentration of insulin used was maintained at 50 mg/dl. After conducting 15 consecutive measurements, the standard deviation of the insulin sample with a concentration of 50 mg/dl was 2.9%, where the coefficient of variation was determined to be 11%. On the other hand, reproducibility pertains to the level of agreement in the measurement results of a method across different days. Based on the conducted experiments, it was observed that when the working electrode is stored at a temperature of +4°C, it can be effectively utilized for a duration of 43 days. After 43 days shelf life duration insulin biosensor yield obtained under the 80%.

Receiver Operating Characteristic (ROC) Analyses

The ROC curve serves multiple purposes, including assessing the discriminatory ability of a test, establishing the optimal positivity threshold, monitoring the accuracy of laboratory findings, and comparing the diagnostic efficacy of different tests (17,18). In our analysis, we found that the area under the ROC curve amounted to 63.3% (Figure 4). It is worth noting that if the area surpasses 50% in the ROC curve analysis, it indicates a successful test outcome.

DISCUSSION

Immobilization Efficiency and Stability

The effectiveness and robustness of immobilization techniques play a vital role in enhancing the stability of bioactive films on substrates (19). Utilizing SAM has been shown to be particularly effective in preventing the detachment of bioreceptors, thereby improving the overall stability of biosensors for prolonged durations. This attribute is essential for ensuring the reliability and longevity of biosensors in real-world applications where long-term sensor stability is imperative (20).

Electrochemical Behavior and Optimization

The precise localization of a particular potential site and the enhancement of the bioactive film are crucial stages in attaining a responsive biosensor that is both sensitive and specific (21). The ideal concentration of 0.2 mg/mL for the insulin tracer protein was determined to be optimal, highlighting the significance of adjusting biosensor elements meticulously to improve overall functionality.

Impact of Physicochemical Conditions

The findings regarding the pH and temperature effects are in line with the established understanding that biosensor responses are highly sensitive to environmental conditions (22,23). The optimal conditions identified for pH and temperature are crucial for maintaining the functional activity and structural integrity of the insulin tracer protein, thereby ensuring accurate biosensor readings.

Analytical Performance

The biosensor's analytical reliability is confirmed through the linear detection range, repeatability, reproducibility, and ROC analysis. The biosensor's potential for consistent

and reliable measurements is highlighted by the defined linear range, high level of repeatability, and reproducibility. Additionally, the ROC analysis serves to validate the biosensor's diagnostic performance, establishing it as a valuable tool in the analytical field (24,25).

CONCLUSION

When compared to existing methods with our electrobiochemical method for insulin determination, our method offers new insights for laboratory diagnosis. Existing traditional methods need some specific and expensive medical devices however bioelectrochemistry offers portable low costs devices. The insulin biosensor we were studied on has the potential to be a reference for new simple-to-use portable/wearable devices for medical use.

Biosensors for insulin offer cost-effective, time-efficient, sensitive, and practical solutions. These studies have demonstrated that biosensors are highly sensitive, specific, straightforward, and valuable techniques, typically utilizing immobilised insulin tracer protein forms. The advancement of biosensor technology has significantly enhanced the efficiency of obtaining economical, practical, specific, and sensitive insulin detection results. The newly developed insulin biosensor shows great potential for utilisation in clinical biochemistry laboratories.

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Conflict of interest: *The authors have no conflicts of interest to declare.*

Ethical approval: *No biological samples from humans or animals were used in the studies. All solutions used are commercially available products. For this reason, ethics committee approval is not required in this study.*

REFERENCES

- Joshi SR, Parikh RM, Das AK. Insulin—history, biochemistry, physiology and pharmacology. *J Assoc Physicians India.* 2007;55:19-25.
- Lian K, Feng H, Liu S, et al, Insulin quantification towards early diagnosis of prediabetes/diabetes. *Biosens Bioelectron.* 2022;203:114029.
- Servarayan L, Sundaram E, Manna A, Sivasamy VV. Label free optical biosensor for insulin using naturally existing chromene mimic synthesized receptors: a greener approach. *Anal Chim Acta.* 2023;1239:340692.
- Lebovitz HE. Insulin: potential negative consequences of early routine use in patients with type 2 diabetes. *Diabetes Care.* 2011;34:S225-30.
- Fu Y, Foden JA, Khayter C, et al, High-frequency off-target mutagenesis induced by CRISPR-Cas nucleases in human cells. *Nat Biotechnol.* 2013;31:822-6.
- Psoma SD, Kanthou C. Wearable insulin biosensors for diabetes management: advances and challenges. *Biosensors (Basel).* 2023;13:719.

7. Zhu X, Chen Y, Feng, C, et al. Assembly of self-cleaning electrode surface for the development of refreshable biosensors. *Anal Chem.* 2017;89:4131-8.
8. Seitz O, Fernandes, PG, Tian R, et al. Control and stability of self-assembled monolayers under biosensing conditions. *Journal of Materials Chemistry.* 2011;21:4384-92.
9. Kökbaş U, Kayrın L, Tuli A. Biosensors and their Medical Applications. *AKTD.* 2013;22:499-513.
10. Kartlaşmış K, Kökbaş U, Kayrın L. Electrochemical characterization of cholesterol biosensor formed by polymer film based on o-Phenylenediamine and benzoquinone. *IGUSABDER.* 2023;347-60.
11. Cutler HB, Madsen S, Masson SW, et al. Dual tracer test to measure tissue-specific insulin action in individual mice identifies in vivo insulin resistance without fasting hyperinsulinemia. *Diabetes.* 2024;73:359-73.
12. Kirk NS, Chen Q, Wu YG, et al. Activation of the human insulin receptor by non-insulin-related peptides. *Nat Commun.* 2022;13:5695.
13. İlhan A, Kökbaş U, & Kayrın L. The effect of different acetate buffer concentrations on enzyme activity in electrochemical studies. *EJONS International Journal on Mathematic, Engineering and Natural Sciences.* 2022;6:293-301.
14. Chadha U, Bhardwaj P, Agarwal R, et al. Recent progress and growth in biosensors technology: a critical review. *Journal of Industrial and Engineering Chemistry.* 2022;109:21-51.
15. Beitollahi H, Mohammadi SZ, Safaei M, Tajik S. Applications of electrochemical sensors and biosensors based on modified screen-printed electrodes: a review. *Analytical Methods.* 2020;12:1547-60.
16. Haleem A, Javaid M, Singh RP, et al. Biosensors applications in medical field: a brief review. *Sensors International.* 2021;2:100100.
17. Cai B, Xia Z, Wang J, et al. Reduced graphene oxide-based field effect transistor biosensors for high-sensitivity mirna21 detection. *ACS Applied Nano Materials.* 2022;5:12035-44.
18. Cui F, Yue Y, Zhang Y, et al. Advancing biosensors with machine learning. *ACS Sens.* 2020;5:3346-64.
19. Hu X, Wang T, Li F, Mao, X. Surface modifications of biomaterials in different applied fields. *RSC Advances.* 2023;13:20495-511.
20. Luong AD, Roy I, Malhotra BD, Luong JH. Analytical and biosensing platforms for insulin: a review. *Sensors and Actuators Reports.* 2021;3:100028.
21. Bermingham KP, Doran MM, Bolger FB, Lowry JP. Design optimisation and characterisation of an amperometric glutamate oxidase-based composite biosensor for neurotransmitter l-glutamic acid. *Anal Chim Acta.* 2022;1224:340205.
22. Drozd M, Kobylska E, Żmieńko M, Chudy M. Sensitive and label-free SPR biosensing platforms for high-throughput screening of plasma membrane receptors interactions with insulin-like targets of hypoglycaemic activity. *Talanta.* 2024;274:125914.
23. Jalalvand AR, Pinto L. A novel triple templates molecularly imprinted biosensor assisted by second-order calibration methods based on generation of second-order hydrodynamic linear sweep voltammetric data for simultaneous biosensing of insulin, proinsulin and C-peptide: application to comparing PARAFAC2 and PARASIAS. *Chemometrics and Intelligent Laboratory Systems.* 2023;233:104746.
24. Nahm, FS. Receiver operating characteristic curve: overview and practical use for clinicians. *Korean J Anesthesiol.* 2022;75:25-36.
25. Roumeliotis S, Schurgers J, Tsalikakis DG, et al. ROC curve analysis: a useful statistic multi-tool in the research of nephrology. *Int Urol Nephrol.* 2024 Mar 26. doi: 10.1007/s11255-024-04022-8. [Epub ahead of print].



Factors Associated with Upper Extremity Functionality After Mini-Open Release Surgery for Treatment of Carpal Tunnel Syndrome

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Abstract

Aim: The objective of this study was to investigate the correlation between upper extremity functionality, pain intensity, muscle strength, and symptom severity among patients diagnosed with carpal tunnel syndrome (CTS) who underwent mini-open release surgery.

Material and Method: This retrospective study entailed the review of medical records of 70 patients diagnosed with CTS who underwent mini-open release surgery between January 2021 and January 2023. Data were collected from preoperative assessments and routine follow-up evaluations conducted at 3 months post-surgery. Upper extremity functionality was assessed utilizing the Disabilities of Arm, Shoulder, and Hand (DASH) questionnaire, pain severity was determined using the Visual Analog Scale (VAS), muscle strength was evaluated through hand grip strength, and disease severity was measured using the Boston Carpal Tunnel Questionnaire (BCTQ).

Results: A statistically significant improvement was observed in DASH questionnaire scores, VAS scores, hand grip strength, and BCTQ scores at the 3-month follow-up compared to preoperative values ($p < 0.05$). Furthermore, significant correlations were found between DASH questionnaire scores and VAS scores, hand grip strength, and BCTQ scores during postoperative assessments ($p < 0.05$).

Conclusion: Mini-open-release surgery demonstrates effectiveness as a surgical approach for achieving favorable clinical outcomes in patients with CTS. Furthermore, our findings suggest that postoperative upper extremity functionality may be influenced by factors such as pain intensity, symptom severity, and hand grip strength. Therefore, we advocate for the integration of these factors into postoperative patient evaluation protocols and treatment programs to optimize patient outcomes.

Keywords: Functionality, carpal tunnel syndrome, treatment, mini-open-release surgery

INTRODUCTION

Carpal tunnel syndrome (CTS) is characterized by symptomatic compression of the median nerve at the wrist level (1). CTS stands out as one of the most prevalent entrapment neuropathies, impacting the upper extremity and leading to constraints in daily activities. Among individuals affected by CTS, sensory manifestations including paresthesia, dysesthesia, muscular weakness in median nerve-innervated muscles, and compromised upper extremity functionality are frequently encountered (2). The prevalence of CTS within the community is estimated to be approximately 8% (3), with an incidence roughly 2-3 times higher in women than in men (4).

Conservative treatments for CTS commonly include the use of wrist splints, anti-inflammatory and analgesic medications, physiotherapy modalities, and occasionally corticosteroid injections into the carpal tunnel (5,6). Surgical decompression techniques are reserved for patients who fail to respond to conservative interventions. These surgical procedures may involve either open or endoscopic approaches. Surgical interventions have been shown to alleviate CTS symptoms in approximately 70–90% of patients (7,8). For instance, Verdugo et al. (9) demonstrated that surgical intervention provides greater relief of symptoms compared to wrist splinting in patients with CTS.

CITATION

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Studies have indicated a correlation between increased compression on the median nerve in individuals with CTS and motor nerve involvement, resulting in symptoms such as hand weakness, diminished function, heightened pain intensity, and atrophy of the thenar region muscles of the hand (10). Consequently, these symptoms lead to a decline in activities of daily living (11), particularly exacerbated by repetitive wrist flexion and extension movements (12). Such impairments have been shown to have a detrimental impact on upper limb functionality and future quality of life (13). Moreover, investigations have highlighted associations between hand functionality, pain severity, and grip strength in patients with CTS (13). Additionally, it has been documented that atrophy of the lumbrical muscles of the 2nd and 3rd fingers during the later stages of CTS leads to hand weakness and a decline in fine motor skills (14).

In the existing literature, studies predominantly focus on investigating factors influencing upper extremity functionality in patients diagnosed with CTS (13,15). However, there are no studies examining the factors related to upper extremity functionality following surgery in CTS patients. Thus, the objective of our study was to investigate the factors associated with upper extremity functionality in patients with CTS who have undergone mini-open release surgery.

MATERIAL AND METHOD

Ethical Aspect and Study Design

Ethical approval for this retrospective and cross-sectional study was granted by the local ethics committee (Number: 5-2024/11), and the research adhered to the principles outlined in the Declaration of Helsinki. In order to use the data, all participants were contacted, and their written and verbal consents were obtained.

Participants

Between January 2021 and January 2023, a retrospective analysis was conducted on 70 patients who underwent mini-open release surgery for unilateral carpal tunnel syndrome (CTS) at the Training and Research Hospital. The analysis included an examination of age, gender, body mass index (BMI), preferred surgical treatment methods, and complications. Patients over 65 years of age, patients who underwent a different surgical intervention, and patients who were included in a postoperative physiotherapy and rehabilitation program were excluded from the study.

Surgical Method

Mini-open release surgery is performed in the following sequence: After regional anesthesia, a 2-3 cm longitudinal incision is made distal to the transverse carpal ligament at the level of the third vein under an arm tourniquet. Subcutaneous adipose tissue and palmar aponeurosis are passed, and the distal transverse carpal ligament is reached. At this time, the superficial palmar arch is visualized and protected. The transverse carpal ligament is checked for motor branch variations. Once the median

nerve is visualized, an Adson forceps handle is positioned between the nerve and the transverse carpal ligament. Then the skin and subcutaneous tissues are excised proximally, and the transverse carpal ligament is opened with scissors from the ulnar side. Finally, the skin is closed by checking the patency of the transverse carpal ligament (16).

Evaluation Tools

Age, gender, body mass index (BMI), and dominant upper extremity designation of the patients were retrieved from their medical records before the commencement of the study. Measurements of the Disabilities of the Arm, Shoulder, and Hand (DASH) Questionnaire, Visual Analog Scale (VAS), hand grip strength, and Boston Carpal Tunnel Questionnaire (BCTQ) scores of patients with CTS were obtained by reviewing patient records both before mini-open release surgery and three months postoperatively.

Upper Extremity Functionality

In the study, the upper extremity functionality of patients with CTS who underwent mini-open release surgery was assessed using the Turkish version of the DASH questionnaire (17). In the study, specifically, we administered the first part of the DASH questionnaire, comprising 30 items on functional status and symptoms. Among these, 21 items assessed challenges in participating in activities of daily living, while 5 items addressed symptoms such as tingling, weakness, stiffness, and pain, and the remaining 4 items explored aspects related to social function, work, sleep, and self-confidence. Each item was rated on a scale from 1 (no difficulty) to 5 (unable to perform), yielding a total score ranging from 0 to 100. A higher score denoted a greater degree of disability (18).

Pain Severity

The pain severity experienced by patients was assessed utilizing the VAS. This scale comprises a 10 cm line, segmented into 10 parts, with each part corresponding to 1 cm. Patients rate their pain level by indicating a point on the line, with a score ranging from 0 (indicating no pain) to 10 (indicating unbearable pain) (19).

Muscle Strength

Hand grip strength was evaluated using a hand dynamometer (Takei, Japan), with measurement positions aligned according to the guidelines provided by the American Association of Hand Therapists. The assessment was conducted on the side affected by CTS. Each measurement was repeated three times, interspersed with a 30-second rest interval between measurements to minimize fatigue. The maximum recorded value in kilograms (kg) was documented for analysis (20).

Symptom Severity

The severity of CTS symptoms was assessed using the Turkish version of the Boston Carpal Tunnel Questionnaire (BCTQ) (21). The questionnaire comprises two parts: the first part, consisting of 11 questions, evaluates symptom severity, while the second part, comprising 8 questions,

assesses functional status. Each question is rated on a scale from 1 (indicating no symptoms) to 5 (indicating very severe symptoms). The total score is calculated by summing the scores from all questions. The score from the first part indicates the severity of symptoms, categorized as: no symptoms (0-11 points), mild symptoms (12-22 points), moderate symptoms (23-33 points), severe symptoms (34-44 points), and very severe symptoms (45-55 points). A higher score reflects greater symptom severity (21). For our study, only the first part of the BCTQ was utilized.

Statistical Analysis

SPSS software was used to perform statistical analyses. A paired sample t-test was used to compare change over time in data that met normal distribution criteria. Factors associated with fatigue severity were evaluated by Pearson correlation analysis in parametric conditions. The correlation degree was interpreted as follows: a correlation coefficient ranging from 0.05 to 0.4 indicated a low correlation, from 0.4 to 0.7 signified a moderate correlation, and from 0.7 to 1.0 denoted a high correlation, based on established correlation coefficients (22).

RESULTS

The demographic data and clinical evaluation of patients with CTS are presented in Table 1. The mean age of patients included in this study was 57.52±5.74 years.

Variables	Mean±SD	Min	Max
Age (years)	57.52±5.74	40.00	65.00
BMI (kg/m ²)	26.81±2.31	21.08	32.38
	n	(%)	
Gender	Male	20	28.6
	Female	50	71.4
Dominant upper extremity	Right	48	68.6
	Left	22	31.4
Side of the surgery	Right	45	64.2
	Left	25	35.8

CTS: carpal tunnel syndrome, SD: standard deviation, Min: minimum, Max: maximum, BMI: body mass index

Table 2 shows the preoperative and postoperative comparison of DASH questionnaire, VAS, hand grip strength, and BCTQ scores among the patients with CTS included in the study. According to the results, when the DASH questionnaire, VAS, hand grip strength, and BCTQ scores of patients with CTS were compared preoperatively and postoperatively, a statistically significant difference was found for all parameters ($p < 0.05$). Thus, it was observed that the treatment method applied was effective on upper extremity functionality, pain, hand grip strength, and symptom severity.

Table 2. Comparison of preoperative and postoperative evaluations of patients with CTS

Variables		CTS (n: 70)	t	p
		Mean±SD		
DASH (score)	Preoperative	70.64±10.71	25.20	<0.001*
	Postoperative	39.72±10.28		
VAS (cm)	Preoperative	5.94±1.00	18.45	<0.001*
	Postoperative	2.52±0.93		
Hand Grip Strength (kg)	Preoperative	9.96±2.84	-12.81	<0.001*
	Postoperative	17.42±2.74		
Boston Carpal Tunnel Questionnaire (score)	Preoperative	42.36±7.06	14.09	<0.001*
	Postoperative	25.88±4.72		

CTS: carpal tunnel syndrome, SD: standard deviation, DASH: disabilities of the arm, shoulder and hand questionnaire, VAS: visual analog scale, t: Paired sample t-test

Table 3 presents the relationship between the DASH questionnaire and VAS, BCTQ, and hand grip strength results among the patients with CTS included in the study. According to this table, a positive, high level statistical relationship was found between the DASH questionnaire results with hand grip strength and BCTQ results of patients with CTS, while a negative, high level statistical relationship was found between the DASH questionnaire results and VAS ($p < 0.05$) (Table 3).

Table 3. Investigation of the relationships between DASH questionnaire and other evaluation parameters in patients with CTS

Variables	DASH (score) (n: 70)
	r (p)
VAS (cm)	0.894 (<0.001*)
Hand Grip Strength (kg)	-0.800 (<0.001*)
Boston Carpal Tunnel Questionnaire (score)	0.786 (<0.001*)

DASH: disabilities of the arm, shoulder and hand questionnaire, CTS: carpal tunnel syndrome, VAS: visual analog scale, r: Pearson correlation coefficient, * $p < 0.001$

DISCUSSION

In this retrospective study, we examined the preoperative and 3-month postoperative status of patients with CTS who underwent mini-open release surgery and the relationship between postoperative upper extremity functionality and pain intensity, hand grip strength, and CTS symptom severity. Our findings show that mini-open release surgery provides significant improvements in pain relief, increased hand grip strength and decreased symptom severity in patients with CTS. Additionally, we observed a high correlation between pain intensity, hand grip strength, and symptom severity with upper extremity functionality following mini-open release surgery.

Mini-open surgical techniques offer expedited recovery of hand function post-surgery in contrast to other methods. These techniques present benefits such as minimal scarring, reduced scar tissue pain, and shorter recovery duration. To mitigate complications and enhance patient functional status, numerous researchers favor mini-open release surgery (23,24). Celocco et al. (25) compared the BCTQ results of proximal mini-open technique and limited open technique. They obtained a significant improvement in symptom severity after treatment in the mini-open technique. While symptom severity improved similarly in both groups, improvement in grip strength and pain level was found in favour of mini-open transverse release surgery (25). Calleja et al. (26) showed that different mini-open release surgical approaches resulted in significant improvements in upper extremity functionality in patients with CTS. Atroschi et al. (27) found that mini-open release surgery showed significant improvements in functional status and pain in patients with CTS. Thoma et al. (28) stated that mini-open release surgery was effective in improving pain and grip strength in patients with CTS. In our study, improvements in upper extremity functionality, pain severity, hand grip strength and symptom severity were observed in patients with CTS after mini-open release surgery, in accordance with the results in the literature. Based on all these findings, it can be said that mini-open release surgery reduces the pressure in the carpal tunnel and the compression on the median nerve, reduces the complaints of the patients and improves their functional status.

Subjective questionnaires are more effective than objective measurements in evaluating the general function and disability of the hand from the patient's perspective (29). In studies, there are conflicting results in terms of the relationship between the increase in the occurrence of clinical symptoms and the severity of electromyography findings (30). Therefore, subjective data are thought to reflect clinical symptoms more.

DASH is guiding in determining the functional status of the upper extremity. It is documented that the DASH questionnaire is a validated, sensitive, and reliable measurement tool (31). Bakhsh et al. (32) evaluated the validity and reliability of the DASH questionnaire and BCTQ in patients with CTS and assessed the relationship between these two questionnaires. They found a strong correlation between functional status and symptom severity. Umay et al. (29) found a strong correlation between upper extremity functional status and symptom severity in individuals with CTS. Akçay et al. (33) examined the relationship between functional status, pain level, and symptom severity in women with CTS. They stated that there was a significant relationship between functional status and symptom severity. In our study, a strong correlation was observed between functional status and symptom severity, consistent with existing literature.

Pain is a prevalent symptom among patients with CTS and exerts a notable impact on functional abilities.

Elevated pain levels result in restrictions in functional status and activities of daily living (13,15). Akçay et al. (33) identified a significant association between pain level and hand functionality in patients with CTS. In our study, we identified a notable relationship between pain intensity and upper extremity functionality among patients with CTS who underwent mini-open release surgery. These findings suggest that pain may cause loss of functional status by causing kinesiophobia. After mini-open release surgery, the reduction of pain with the reduction of pressure on the median nerve may have been effective in the improvement of the upper extremity functionality of the patients.

The presence of tenar atrophy, which is one of the important symptoms of CTS, negatively affects muscle strength and thus grip strength. Singh et al. (34) examined the relationship between disease severity and grip strength in patients with CTS. They stated that grip strength decreased as the severity of symptoms increased (34). The effects of upper extremity muscle strength on functionality in women with CTS were investigated. In this study, it was stated that muscle strength was affected in patients with CTS, and the DASH questionnaire score and grip strength were related (15). Ise et al. (35) found a significant correlation between grip strength and functionality after release surgery in patients with CTS. In our study, a strong relationship between functional status and grip strength was observed in accordance with the literature. It can be said that the decrease in the complaints of the patients after surgery is effective in increasing the muscle strength and this positively affects the upper extremity functionality.

To the authors' knowledge, this study represents the first investigation into the factors influencing upper extremity functionality following mini-open release surgery in patients with CTS. In this regard, we assert that the findings of this study, which we anticipate will offer valuable contributions to the literature, hold significance.

Our study has several limitations. Firstly, no gender-based evaluation was performed in our study. Secondly, our study only analyzed the factors associated with upper extremity functionality after mini-open release surgery. In future studies, we think that gender-based evaluation and factors associated with upper extremity functionality after different surgical techniques should be examined.

CONCLUSION

To the best of our knowledge, the present study is the first study to examine the factors associated with upper extremity functionality after mini-open release surgery in patients with CTS. In this respect, it is thought that the findings of the current study are important and will make important contributions to the literature. It can be concluded that increased pain and symptom severity and decreased hand grip strength are effective in worsening upper extremity functionality in patients with CTS. On the other hand, mini-open release surgery may be effective in improving upper extremity functionality by reducing pain and symptom severity and increasing hand grip strength

in patients with CTS. We think that it may be useful to consider the results of the this study in future research and clinical practice in patients with CTS.

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REFERENCES

1. Keith MW, Masear V, Chung KC, et al. American academy of orthopaedic surgeons clinical practice guideline on: diagnosis of carpal tunnel syndrome. *J Bone Joint Surg Am.* 2009;91:2478-9.
2. Neal SL, Fields KB. Peripheral nerve entrapment and injury in the upper extremity. *Am Fam Physician.* 2010;81:147-55.
3. Luckhaupt SE, Dahlhamer JM, Ward BW, et al. Prevalence and work-relatedness of carpal tunnel syndrome in the working population, United States, 2010 national health interview survey. *Am J Ind Med.* 2013;56:615-24.
4. Mitake T, Iwatsuki K, Hirata H. Differences in characteristics of carpal tunnel syndrome between male and female patients. *J Orthop Sci.* 2020;25:843-6.
5. Katz JN, Losina E, Amick III BC, et al. Predictors of outcomes of carpal tunnel release. *Arthritis Rheum.* 2001;44:1184-93.
6. Bobowik PŽ. Effectiveness of physiotherapy in carpal tunnel syndrome (CTS). *Advances in Rehabilitation.* 2019;33:47-58.
7. Hybbinette C-H, Mannerfelt L. The carpal tunnel syndrome: a retrospective study of iOQ operated patients. *Acta Orthop Scand.* 1975;46:610-20.
8. Kulick MI, Gordillo G, Javidi T, et al. Long-term analysis of patients having surgical treatment for carpal tunnel syndrome. *J Hand Surg Am.* 1986;11:59-66.
9. Verdugo RJ, Salinas RA, Castillo JL, Cea G. Surgical versus non-surgical treatment for carpal tunnel syndrome. *Cochrane Database Syst Rev.* 2008;CD001552.
10. You H, Simmons Z, Freivalds A, et al. Relationships between clinical symptom severity scales and nerve conduction measures in carpal tunnel syndrome. *Muscle Nerve.* 1999;22:497-501.
11. Burger M, Kriel R, Damon A, et al. The effectiveness of low-level laser therapy on pain, self-reported hand function, and grip strength compared to placebo or "sham" treatment for adults with carpal tunnel syndrome: a systematic review. *Physiother Theory Pract.* 2017;33:184-97.
12. Arroari S, Spence A. Roy, carpal tunnel syndrome. *Ulster Med J.* 2008;77:6-17.
13. Nazari G, Shah N, MacDermid JC, Woodhouse L. The impact of sensory, motor and pain impairments on patient-reported and performance based function in carpal tunnel syndrome. *Open Orthop J.* 2017;11:1258-67.
14. Kürklü M, Türkkan S, Tüzün HY. Carpal tunnel syndrome and other entrapment neuropathies of the median nerve. *TOTBİD Dergisi.* 2015;14:566-71.
15. Keskinöz PC, Ergin G, Bakırhan S, Özden A. Does muscular strength and endurance affect the functions of the upper extremity in patients with carpal tunnel syndrome?. *Turkish Journal of Physiotherapy and Rehabilitation.* 2020;31:58-65.
16. Cellocco P, Rossi C, Bizzarri F, et al. Mini-open blind procedure versus limited open technique for carpal tunnel release: a 30-month follow-up study. *J Hand Surg Am.* 2005;30:493-9.
17. Düger T, Yakut E, Öksüz Ç, et al. Kol, omuz ve el sorunları (disabilities of the arm, shoulder and hand-DASH) anketi Türkçe uyarlamasının güvenilirliği ve geçerliği. *Fizyoterapi Rehabilitasyon.* 2006;17:99-107.
18. Hudak PL, Amadio PC, Bombardier C, et al. Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder, and head). *Am J Ind Med.* 1996;29:602-8. Erratum in: *Am J Ind Med* 1996;30:372.
19. Bijur PE, Silver W, Gallagher EJ. Reliability of the visual analog scale for measurement of acute pain. *Acad Emerg Med.* 2001;8:1153-7.
20. Shechtman O, Gestewitz L, Kimble C. Reliability and validity of the DynEx dynamometer. *J Hand Ther.* 2005;18:339-47.
21. Sezgin M, İncel NA, Sevim S, et al. Assessment of symptom severity and functional status in patients with carpal tunnel syndrome: reliability and validity of the Turkish version of the Boston Questionnaire. *Disabil Rehabil.* 2006;28:1281-5.
22. Schober P, Boer C, Schwarte LA. Correlation coefficients: appropriate use and interpretation. *Anesth Analg.* 2018;126:1763-8.
23. van den Broeke LR, Theuvenet WJ, van Wingerden JJ. Effectiveness of mini-open carpal tunnel release: an outcome study. *Arch Plast Surg.* 2019;46:350-8.
24. Bai J, Kong L, Zhao H, et al. Carpal tunnel release with a new mini-incision approach versus a conventional approach, a retrospective cohort study. *Int J Surg.* 2018;52:105-9.
25. Muhammed Fazil VV, Surendran S, Karuppal R, et al. Mini-open transverse flexor crease incision versus limited longitudinal palmar incision carpal tunnel release: a short term outcome study. *J Orthop.* 2022;29:15-21.
26. Calleja H, Tsai T-M, Kaufman C. Carpal tunnel release using the radial sided approach compared with the two-incision approach. *Hand Surg.* 2014;19:375-80.
27. Atroshi I, Larsson G-U, Ornstein E, et al. Outcomes of endoscopic surgery compared with open surgery for carpal tunnel syndrome among employed patients: randomised controlled trial. *BMJ.* 2006;332:1473.
28. Thoma A, Veltri K, Haines T, Duku E. A meta-analysis of randomized controlled trials comparing endoscopic and open carpal tunnel decompression. *Plast Reconstr Surg.* 2004;114:1137-46.
29. Umay E, Karaahmet ZÖ, Avluk Ö, et al. Relationship between the severity of compression and clinical symptoms, physical, functional and quality of life findings in patients with carpal tunnel syndrome. *Turk J Phys Med Rehab.* 2011;57:193-200.

30. Tamburin S, Cacciatori C, Marani S, Zanette G. Pain and motor function in carpal tunnel syndrome: a clinical, neurophysiological and psychophysical study. *J Neurol*. 2008;255:1636-43.
31. Greenslade J, Mehta R, Belward P, Warwick D. Dash and Boston questionnaire assessment of carpal tunnel syndrome outcome: what is the responsiveness of an outcome questionnaire?. *J Hand Surg Br*. 2004;29:159-64.
32. Bakhsh H, Ibrahim I, Khan W, et al. Assessment of validity, reliability, responsiveness and bias of three commonly used patient-reported outcome measures in carpal tunnel syndrome. *Ortop Traumatol Rehabil*. 2012;14:335-40.
33. Akçay İH, Demirdel E. The investigation of the results of clinical evaluation, pain, functional status and sleep quality according to electrodiagnostic test results in females with carpal tunnel syndrome: a pilot study. *IGUSABDER*. 2022;526-39.
34. Singh GK, Srivastava S. Grip strength of occupational workers in relation to carpal tunnel syndrome and individual factors. *Int J Occup Saf Ergon*. 2020;26:296-302.
35. Ise M, Saito T, Katayama Y, et al. Relationship between clinical outcomes and nerve conduction studies before and after surgery in patients with carpal tunnel syndrome. *BMC Musculoskelet Disord*. 2021;22:882.



Investigation of the Relationship Between Cervical Vertebral Column Degeneration and Posterior Circulation Perfusion Area Ischemia

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Abstract

Aim: The primary objective of this study was to establish whether degeneration of the cervical vertebrae and paravertebral structures serves as a predisposing factor for ischemic processes by disrupting hemodynamics in the posterior system through mechanical effects on the vertebral arteries.

Material and Method: We conducted a retrospective analysis of 180 patients who underwent various imaging tests between January 2017 and October 2023. These tests included cervical magnetic resonance imaging (MRI), cervical computed tomography (CT), carotid-vertebral neck CT angiography (CTA), cranial CT, and cranial MRI. Of the 180 patients, 90 had mild degeneration or no significant degeneration, with a mean age of 58 years, and 90 had significant cervical spondylosis (CS) with a mean age of 64 years. The radiological findings were statistically analyzed, and a p-value of less than 0.05 was considered statistically significant.

Results: There was no significant difference between age and parenchymal density in the control group ($p=0.09$). There was no statistically significant difference between the age and parenchymal density in the CS group ($p=0.07$). As CS became more severe, there was a statistically significant increase in the incidence of atrophic enlargement of the cerebellar folia and loss of density in the posterior fossa ($p=0.03$) and posterior circulation infarcts (POCI) ($p=0.04$).

Conclusion: When severe, CS can adversely affect vascular hemodynamics in the posterior system, predisposing perfused neural parenchyma to ischemia.

Keywords: Paravertebral structures, posterior circulation, vertebrae degeneration, vertebral artery

INTRODUCTION

Spinal degeneration is terminologically defined as "spondylosis" (1,2). Cervical spondylosis (CS) is typically observed in middle-aged and elderly individuals. It is the most common cause of progressive spinal cord and nerve root compression (3,4). The majority of patients with CS are asymptomatic, and the most common initial finding in symptomatic patients is neck pain and limitation of neck movement, which occur due to cervical misalignment and neural compression (5). Patients usually do not know the exact time of onset of symptoms (6). The most common complaint is weakness and loss of dexterity in the upper extremities (7).

Acute ischemic stroke in young patients is often attributed to arterial dissections (8). In contrast, the chronic ischemic processes observed in middle-aged and elderly patients may be caused by the narrowing of the arteries due to atherosclerosis, compression of the external lumen due to

degeneration, and hemodynamic negativities in addition to secondary stenosis (9). The vertebral artery originates from the posterior superior part of the subclavian artery on both sides, enters the transverse foramen at the level of the C6 cervical spine (7.5% from C7), and extends upward within these canals (10). The widespread use of radiological imaging modalities has revealed the more frequent occurrence of chronic ischemic findings in the neural parenchyma of the posterior fossa perfused by the posterior circulation in middle-aged and elderly populations (11,12).

In cases of severe CS, the vertebral artery may not be compressed significantly when the patient is stable, or even if it is compressed, the arterial system originating from the posterior circulation and perfused neural parenchyma may compensate for the hemodynamic abnormality in the long term. However, since the cervical spine is a highly unstable and mobile anatomical body part in daily life, the compression to which the vertebral arteries may be

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exposed may change rapidly. Therefore, the autonomic nervous system may not be able to compensate for the lack of perfusion that may result from this (13).

In our study, we aimed to quantitatively determine the chronic ischemic process that may be caused by hemodynamic disturbances originating from the vertebrobasilar system in patients with CS by qualitatively detecting ischemic areas in the posterior fossa on cranial MRI and measuring the density in Hounsfield Units (HU) on computed tomography (CT) from the same location.

MATERIAL AND METHOD

Ethics Committee Approval

Our study was conducted at the Department of Radiology of BHT Clinic İstanbul Tema Hospital, with the approval and permission of the Academic Board and Ethics Committee of Nişantaşı University (date: 14.08.2023, decision No: 13). Our study was retrospectively based on radiologic imaging evaluation, and the procedures were performed in accordance with the Declaration of Helsinki and its amendments.

Study Population

This study included cervical magnetic resonance imaging (MRI), cervical CT, neck CT angiography (CTA), and radiological images of 180 patients who underwent concurrent brain CT and brain MRI examinations between January 2017 and October 2023. Poor quality images were excluded. Patients with a history of intracranial surgery, severe cerebral ischemia, cerebral hemorrhage, vertebral artery occlusion, and/or significant stenosis were excluded. Patients examined between January 2017 and October 2023 were screened according to inclusion and exclusion criteria. Data collection was initiated for 180 eligible patients.

Ninety patients with mild or no significant degeneration were included in the control group, with a mean age of 58 years. In this group, 44 were female and 46 were male; the youngest was 48 years old and the oldest was 62 years old (Table 1).

The remaining 90 patients had moderate and prominent CS, 40 of whom were female and 50 were male with a mean age of 64 years. The youngest patient in this group was 56 years old, and the oldest was 66 years old (Table 1).

Table 1. Age and gender distribution of patients		
Patients	Control group	CS
Gender	Female/male	
	44/46	40/50
Age(years)	Minimum/maximum	
	48/62	56/66
	Mean	
	58	66

CS: cervical spondylosis

Obtaining Radiologic Images and Study Design

The images of the patients included in our study were retrospectively evaluated using a radiological image

storage system (picture archiving and communication system, PACS) at the hospital where the study was performed. There were 2 CT devices used in the hospital, the first was a General Electric (GE) Brightspeed 16 detector Multislice CT (GE, Waukesha, Wisconsin, USA) and the second was a GE Revolution GSI 256 detector Multislice CT (GE, Waukesha, Wisconsin, USA). Similarly, the patients examined in our study were examined using two MRI devices, the first of which was a GE Signa HDe 1.5 Tesla (GE, Waukesha, Wisconsin, USA). Coil: HD 8 channel NV array coil (In vivo Corporation, Gainesville, Florida, USA)). Our second device had more advanced features: GE Signa Architect 3 Tesla (GE, Waukesha, Wisconsin, USA). Coil: 3.0T GEM HNU 19HN+PA NV coil (GE, Aurora, Ohio, USA)). There was no significant difference between these two different CT and MRI devices in terms of their performance and capacity to evaluate patients, detect pathologies, and measure quantitative values in terms of CT density.

Radiologic images of patients who were examined between January 2017 and October 2023 were transferred from the hospital closed-circuit image storage network to the software interface Clear Canvas via PACS and evaluated retrospectively.

Cervical CT and neck CTA images were evaluated using multiplanar reconstruction (MPR) on axial (normal raw data), sagittal, and coronal (MPR-enhanced plans) images. In the CT examinations, osteophyte and facet hypertrophy, especially of bony origin, were evaluated.

In cervical MRI examination, standard sagittal spin echo (SE) T1 and T2 and axial SE T2 sequences were obtained. Uncovertebral degeneration and degenerative findings in the ligaments and paravertebral soft tissues were evaluated using MRI.

Vertebral corpus corner osteophytic tapering and degenerative signal changes in the endplates (classified by Modic typing) on MRI examination are indicative of cervical degeneration.

Modic Degeneration Changes are Divided into Three Types

In the type 1 cases, edema and inflammation were observed in the bone marrow. In type 2, normal bone marrow cells are transformed into yellow fatty bone marrow cells due to ischemia. Type 3 indicates subchondral bone sclerosis. In addition, mixed types, in which type 1, type 2, type 2, and type 3 are observed together may also be observed (14).

We classified the patients with spinal degeneration as mild, moderate, or severe. We classified patients with mild degeneration as those with minimal cervical osteophytes at only one or a few vertebral levels, Schmorl's nodules on vertebral endplates, and mild degenerative signal changes on MRI (especially Modic type 1 and type 2 degeneration). These patients exhibited minimal degenerative changes in the intervertebral discs at one or two levels. Those with moderate degeneration included those with significant flattening of the cervical lordosis at the level of three to four vertebrae, osteophytes involving the anterior

longitudinal ligament (ALL) and occasionally extending into the spinal canal, and degenerative changes in the facet joints. In addition, cervical MRI scans of these patients mostly showed Modic type 2 degeneration. In terms of intervertebral disc degeneration, mild volume loss at two or three levels and signal loss on MRI T2 sequence were observed. Patients with severe degeneration showed degeneration at almost all the vertebral levels. In addition, cervical lordosis was mostly reversed and kyphosis developed in these patients. In addition, syndesmophyte formation was present at all levels, ALL was largely eliminated, and intervertebral disc degeneration and herniation were present at almost all levels. Although not relevant, a narrow canal (cervical spinal stenosis) was present. Some patients could not be fully classified and were included in the group in which the characteristics of the group were more predominant, and the difficulty caused by this situation is expressed in the limitations section.

The patients in the control group were mostly normal and had mild, if any, spondylosis (Figure 1), whereas the other 90 patients in the pathology sample of the study had moderate (Figure 2) and severe (Figure 3) CS.

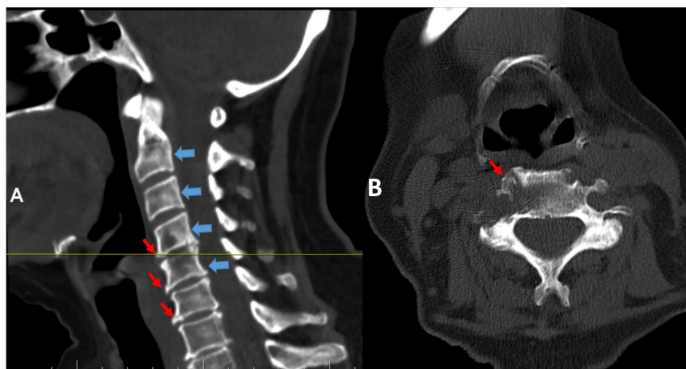


Figure 1. Cervical CT image of one patient. Left (A) is a cervical CT image obtained by MPR in the sagittal plane and right (B) is a cervical CT section image in the axial plane. Examination was performed using a bone window. In A, the thin horizontal yellow line indicates the level of the slice on the right side. In images A and B, the red arrows indicate the cervical osteophytes. When the blue arrows are followed in A, it is observed that the cervical lordosis is flattened. These findings were consistent with mild cervical degenerative changes.

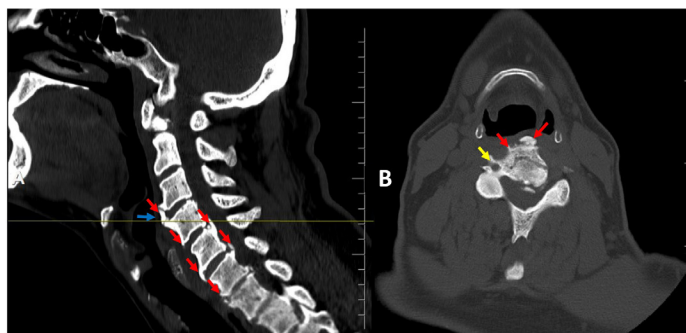


Figure 2. Cervical CT image of one patient. Left (A) shows a cervical CT image obtained by MPR in the sagittal plane and right (B) shows a cervical CT slice image in the axial plane. Examination was performed using a bone window. In A, the thin horizontal yellow line indicates the level of the slice on the right side. The red arrows in panels A and B indicate cervical osteophytes. The blue arrow in A indicates the ALL with an elongated appearance. B, Yellow arrow indicates the transverse foramen. These findings were consistent with moderate cervical degenerative changes.



Figure 3. Cervical CT image of one patient. Left (A) is a cervical CT image obtained by MPR in the sagittal plane and right (B) is a cervical CT section image in the axial plane. Examination was performed using a bone window. In A, the yellow line indicates the level of the slice on the right-hand side. In images A and B, the red arrows indicate the cervical osteophytes. In A, the green arrows indicate syndesmophytes. B, Yellow arrow indicates the transverse foramen. These findings are consistent with those of advanced cervical degenerative changes.

The vertebral arteries of the patients were evaluated using axial raw images and MPR sagittal and coronal images derived from contrast-enhanced neck CTA scans (Figure 4).

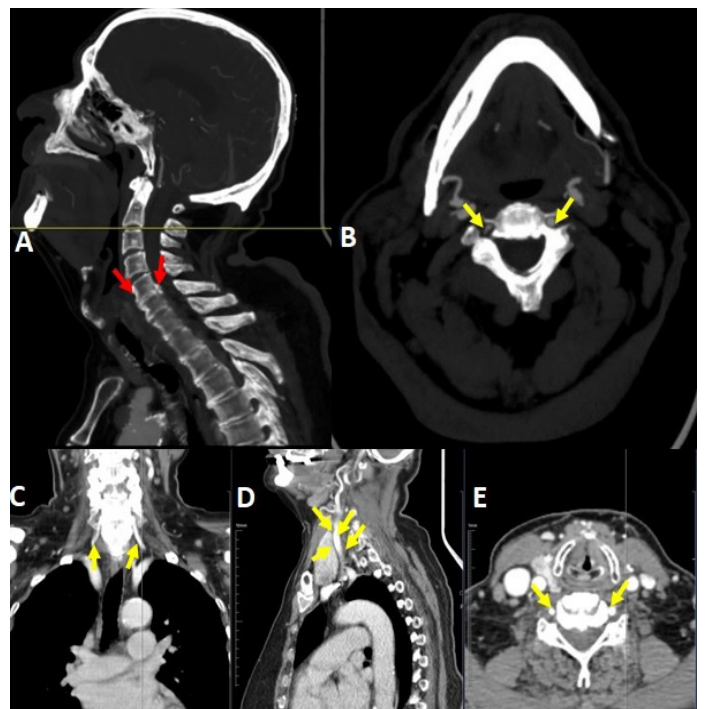


Figure 4. Cervical CTA images of two patients. The top images are of one patient and the bottom images are of another patient. Above; left (A) is a cervical neck CTA image obtained by MPR in the sagittal plane and right (B) is a cross-sectional image in the axial plane. Arteries were evaluated in the vascular window on CTA; however, we chose an intermediate window setting to evaluate both bone degeneration and arteries in these two images. In A, the thin horizontal yellow line indicates the level of the slice on the right and the red arrows indicate osteophytic degeneration at the vertebral corners. In B, yellow arrows indicate the contrast-filled vertebral arteries within the transverse foramen. In the images below, MPR images in C. coronal and D. sagittal planes, and E. axial raw images in the vascular window, from left to right, with yellow arrows pointing to the vertebral arteries.

Similarly, osteodegenerative findings were found on cervical MRI examinations, and MRI had a higher image resolution in soft tissues (paraspinal ligaments and muscles) (Figure 5).

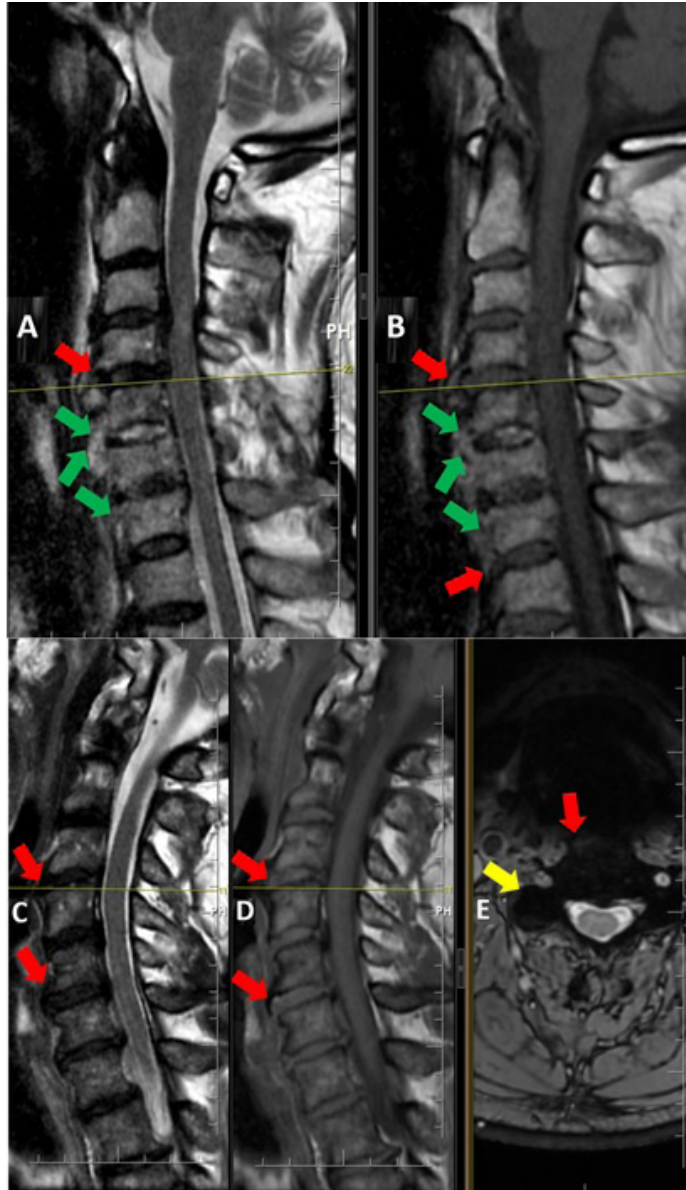


Figure 5. Cervical MRI images of the two patients. The top images are of one patient, and the bottom images are of another patient; the top two sagittal plane images (A. SE T2 and B. SE T1 sequences), red arrows indicate osteophytes, and green arrows indicate syndemophytes. On the basis of these features, this was a case of advanced degeneration. The lower image (C. SE sagittal plane T2, D. SE sagittal plane T1, and E. SE axial plane T2) is of a patient with moderate spondylosis; red arrows indicate osteophytes, and yellow arrow indicates degeneration in the right facet joint (SE: Spin echo).

All patients in the control group had conventional cervical CT and MRI and were evaluated on the basis of these examinations. CTA was not available for all patients in this group. In this group, there were no radiologic degeneration findings that could potentially cause significant compression of the transverse foramen and thus the vertebral arteries.

In the group of patients with moderate and severe

degeneration, CTA examinations of all patients were available and the condition of the vertebral arteries was evaluated. Thus, by excluding patients with direct ischemia, such as critical stenosis and occlusion in the vertebral artery, we were able to exclude patients that should be excluded in order to be able to construct a study on the hypothesis of the negative effect of the dynamic process due to degeneration of vertebral artery hemodynamics, which is the main argument of the study.

Quantitative examination was performed using CT. On cranial CT examinations, HU units were measured from the neural parenchyma in the posterior fossae of patients with moderate and severe degeneration in terms of cervical spondylosis, from the widest location to include the cerebellum and brainstem. HU values were quantitatively measured in the control group. In HU measurements, the largest region was selected in the cerebellar hemispheres so that the white and gray matter of the hemisphere would be included in the measurement area, and the 4th ventricle and transverse sinuses would be spared from the measurement area, which was ensured to be of equal size in all patients for standardization; this area was approximately 7 cm². Similarly, the largest area that could be measured from the brain stem was measured from an area of 3 cm² in all patients in order to measure and standardize the largest area that could be measured. (Figures 6A).

Qualitative evaluations were performed using cranial CT and MRI. In addition to measuring density on CT, both CT and MRI were used to assess folium enlargement and volume loss, which represent cerebellar atrophy. Cerebellar atrophy was considered mild if the enlargement of the cerebellar folia was very mild and there was no significant volume loss, moderate if the cerebellar folia were more prominent and volume loss was also observed, and severe if there was a marked atrophic appearance (15). In addition, hypodense foci observed in the neural parenchymal area of the posterior fossa were considered. The appearance of these areas on MRI was also evaluated in terms of millimetric cerebrospinal fluid lacunes and increased signal in the periphery on T2 sequence images (especially fluid-attenuated inversion recovery [FLAIR]), which may be compatible with chronic lacunar infarction and/or gliosis, depending on the state of ischemia. Chronic lacunar infarcts were usually found in patients with moderate-to-severe chronic ischemia (Figure 6B). These were posterior circulation infarct (POCI) findings. Data were collected and categorized as described above and statistical analyses were performed.

Statistical analyses: All statistical analyses, subject to a significance threshold of $p < 0.05$, were conducted using IBM SPSS for Windows (version 25.0; IBM Corp., NY, USA). Pearson, Spearman, or point-biserial correlation coefficients were calculated as appropriate to explore the relationships between the variables and HU on CT.

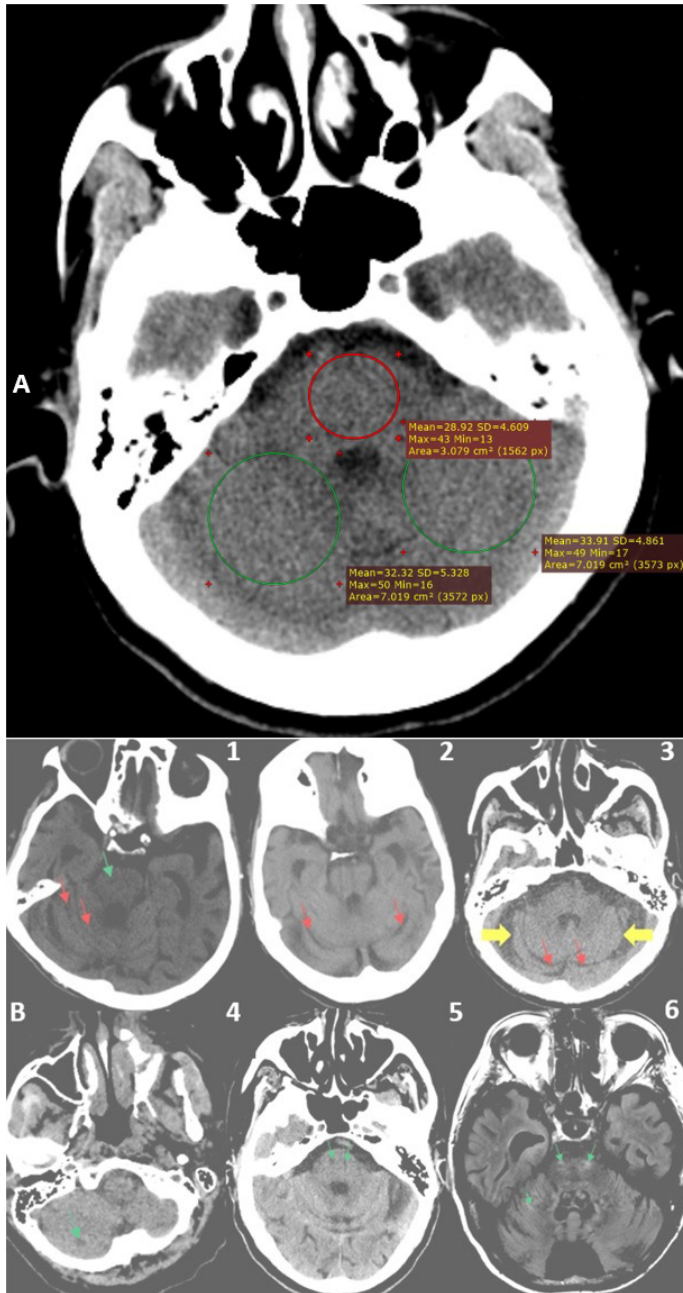


Figure 6. Examples of different cranial CT and MRI examinations in seven patients and HU measurement techniques in the posterior fossa on CT. Top image **A** shows density measurements in the brainstem and cerebellar hemispheres. In the lower **B** images, 1 shows a possible chronic ischemic focus in the brainstem (green arrow) in a patient with mild cerebellar atrophy (red arrows indicate marked reduction in folia). Figure 2 shows a case with more pronounced enlargement of cerebellar folia (red arrows indicate marked enlargement of the folia). Three showed an even more prominent enlargement of the cerebellar folicles (red arrows point to the prominent enlargement of the folia), and in this case, volume loss of the cerebellum was evident (yellow arrows point to the borders of the atrophic cerebellum with reduced volume). In image 4, foci of chronic ischemia in the right cerebellar hemisphere, and in image 5, foci in the brainstem are marked with green arrows. In image 6, foci of chronic lacunar infarction in the brainstem and the right middle cerebellar peduncle are marked with green arrows. These are the POCI findings.

RESULTS

Vertebral artery asymmetry was observed in 43 patients of the control group. The images in A and B in Figure 4 are from one such case. In 10 of these patients, asymmetry was

prominent, the side with thin caliber was dominant, and the other side was hypoplastic (Table 2). However, the patients were asymptomatic. The HU values in these patients were within the normal range. From this perspective, unilateral hypoplasia of the vertebral artery does not cause an ischemic process under normal conditions. The site of vertebral artery hypoplasia has no effect on the ischemic processes. However, in patients with unilateral vertebral artery hypoplasia, atrophic changes, loss of density, and POCI findings in the neural parenchyma in the posterior fossa became statistically more prominent as the CS increased ($p=0.02$) (Table 2).

Table 2. Anatomical structure-variations of vertebral arteries and comparison of HU values of patients with and without unilateral hypoplastic vertebral artery

Control group		CS	
Symmetrical	Dominant-hypoplastic	Symmetrical	Dominant-hypoplastic
47	43	51	39
Severely hypoplastic		Severely hypoplastic	
10		8	
$p=0.02$			
CS: cervical spondylosis, p: Pearson correlation coefficient			

Increased tissue ischemia is directly associated with aging. Therefore, it is expected that the CT density of the tissue in the cerebral parenchyma will decrease after a certain point with increasing age. In our control group, the highest HU was 26 and the lowest HU was 24. There was no statistically significant decrease in the HU values of the neural parenchyma of the posterior fossa with increasing age ($p=0.09$) (Table 3).

Table 3. Statistical correlation between the characteristics of the patients and HU values

Control group	
Age	HU
$p=0.09$	
CS	
Age	HU
$p=0.07$	
CS severity	HU
$p=0.03$	
CS severity	Cerebellar atrophy and POCI
$p=0.04$	
CS: cervical spondylosis, p: Pearson correlation coefficient	

Among the 90 patients with CS findings in the pathological sample, 39 had asymmetry in the vertebral arteries. The images in C, D, and E in Figure 4 are from one such case. In eight of these patients, the asymmetry was quite prominent and the artery contralateral to the dominant side was highly hypoplastic with an extremely thin caliber (Table 2).

In our pathological sample group, which constituted the main population of the study, the highest HU value was 23 and the lowest HU value was 17. There was no significant correlation between HU values of the neural parenchyma of the posterior fossa and increasing age ($p=0.07$) (Table 3).

The cumulative mean HU values in the cerebellum and brainstem decreased significantly as the severity of degeneration of the cervical vertebral column increased ($p=0.03$). Similarly, as the degree of CS progressed, the frequency of cerebellar atrophy and POCI findings increased significantly ($p=0.04$) (Table 3).

Both quantitative HU values measured on CT and qualitative findings of cerebellar atrophy and POCI on CT and MRI were statistically compared between the control group and patients with moderate-to-advanced degeneration. As a result of this analysis, both HU values were lower ($p=0.02$) and qualitative findings were more pronounced ($p=0.04$) in the study population (Table 4).

Table 4. Statistical comparison of the control group and patients with moderate and advanced degeneration in terms of HU and POCI

	Control group	CS
HU		$p=0.02$
Cerebellar atrophy and POCI		$p=0.04$
CS: cervical spondylosis, p: Pearson correlation coefficient		

DISCUSSION

The main idea of our study is based on the idea that hemodynamic disturbances may occur dynamically during neck movements in daily life. In cases of mild CS, there is usually no possibility of external compression of the vertebral arteries by osteophytes. In patients with moderate degeneration, vertebral artery compression may be observed due to osteophytes at one or more levels and/or degeneration in the unvertebral joints and facet arthrosis. In cases of severe degeneration, there are multiple levels of osteophyte-complicated joint and disc degeneration, ligament thickening and calcification, and even syndesmophytes, and usually bilateral foramen transversarium stenosis and possible vertebral artery stenosis secondary to this. These stenoses may not be detected on a cross-sectional image at first glance.

Spinal degeneration is classified according to narrowing of the spinal canal and compression of the spinal cord, especially in the cervical region. As we did not evaluate the patients from this point of view, we made a classification according to the compressibility of the vertebral arteries secondary to degeneration in the dynamic process by determining the framework, albeit qualitatively. Our study was based on the possibility that hemodynamics may be disrupted by neck movements, even in the absence of significant static stenosis in the vertebral arteries. The vertebral column has an intricate anatomical relationship with the vertebrae and paravertebral tissues in a compact space, particularly in the spinal region (15).

CS is a clinical condition that increases in severity with age. However, this does not always occur with age. In some patients, bone structure, metabolic processes, and lifestyle predispose them to degeneration. Moderate or advanced degeneration is observed in middle-aged patients, whereas in others, mild degeneration may be observed even if they are quite old (16,17). Some of our patients had moderate degeneration findings despite being in the middle-aged group and mild degeneration findings despite being in the advanced age group.

Vertebral arteries are arterial vascular structures that are vulnerable to atherosclerosis because of their relatively narrow lumen diameters, emergence from the subclavian artery as a steep branch, sharp kinks in their course, tortuosity in many locations, and long course (18,19). If external luminal compression secondary to cervical degeneration is added to the critical stenosis, a decrease in perfusion in the posterior circulation area is inevitable. Particularly in the elderly population, the incidence and severity of atherosclerosis and CS increase, and the deterioration of hemodynamics creates a predisposition to this condition at later ages (20,21).

In our study, we investigated whether the hemodynamics of the posterior circulation, that is, the vertebrobasilar system, are impaired due to movement in the background of CS. There is insufficient data on this subject in the literature. Studies in the literature generally aim to investigate acute ischemic processes related to static stenosis in the vertebrobasilar system or chronic ischemic changes secondary to stenosis. Therefore, in the literature, acute vertebrobasilar insufficiency developed in conditions such as trauma, dissection, and chronic ischemic processes due to stenoses caused by atherosclerotic changes in the vertebral lumens or stenoses developed due to external compression of the lumen predominate (22-28). In our study, we attempted to detect ischemic processes caused by vertebrobasilar insufficiency secondary to dynamic and frequent compression of the vertebral arteries due to neck movements, although no critical stenosis was observed on static examination.

Although acute disturbances in hemodynamics are tolerable, damaging effects may occur when chronic and persistent abnormalities develop, even in small amounts (29,30).

According to the literature, the HU value of gray matter in normal cerebral parenchyma is approximately 35 and that of white matter is approximately 25 (31). Based on this information, it would not be incorrect to express a mean value of 30 HU. In our measurements, we aimed to examine the cerebellar hemisphere and brainstem in a manner that covers both components at nearly equal rates. The HU values of our patients in the control group ranged from 24-36 with a mean of 27, which is approximately in agreement with the data in the literature. In the group that constituted the main population of our study, we found a minimum HU of 17 and maximum HU of 23. The cumulative decrease in these values was probably

secondary to the ischemic processes caused by CS, as determined statistically.

Study Limitations

One of our most important limitations is that the patients were not analyzed in terms of hypertension, diabetes, and cardiovascular disease status. While classifying the cases in terms of spondylosis, the grouping of some cases was not completely clear, and they were included in whichever group was predominant. Another limitation is the difficulty of measuring HU on CT examination; in other words, the value obtained may not be reliable. Artifacts caused by the calvarial bones in the posterior fossa may cause this situation. Another limitation is the possibility that fluctuations in blood pressure may also contribute to hemodynamic disturbances. The small number of cases is also a limitation.

In our study, when the qualitative and quantitative findings of the control group and the group considered pathological were compared statistically, the results supporting chronic ischemia were found at a higher rate in cases with moderate and advanced CS, in terms of both parameters.

CONCLUSION

Although cervical vertebral column degeneration is not acutely symptomatic, it can cause long-term ischemia in the neural parenchyma in this region by adversely affecting perfusion in the posterior system, with recurrent micro-hemodynamic disturbances through the vertebral arteries.

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REFERENCES

- Theodore N. Degenerative cervical spondylosis. *N Engl J Med.* 2020;383:159-68.
- Jitin B. Cervical spondylosis and atypical symptoms. *Neurol India.* 2021;69:602-3.
- Naderi S, Ozgen S, Pamir MN, et al. Cervical spondylotic myelopathy: surgical results and factors affecting prognosis. *Neurosurgery.* 1998;43:43-50.
- Bogduk N, Mercer S. Biomechanics of the cervical spine. I: Normal kinematics. *Clin Biomech (Bristol, Avon).* 2000;15:633-48.
- Sharma R, Garg K, Agrawal S, et al. Atypical symptoms of cervical spondylosis: is anterior cervical discectomy and fusion useful? - an institutional experience. *Neurol India.* 2021;69:595-601.
- Swagerty DL Jr. Cervical spondylotic myelopathy: a cause of gait disturbance and falls in the elderly. *Kans Med.* 1994;95:226-9.
- Montgomery DM, Brower RS. Cervical spondylotic myelopathy. Clinical syndrome and natural history. *Orthop Clin North Am.* 1992;23:487-93.
- Ullberg T, Zia E, Petersson J, Norrving B. Changes in functional outcome over the first year after stroke: an observational study from the Swedish stroke register. *Stroke.* 2015;46:389-94.
- Ng SC, Weiss JB, Quennel R, Jayson MI. Abnormal connective tissue degrading enzyme patterns in prolapsed intervertebral discs. *Spine (Phila Pa 1976).* 1986;11:695-701.
- Caldemeyer KS, Carrico JB, Mathews VP. The radiology and embryology of anomalous arteries of the head and neck. *AJR Am J Roentgenol.* 1998;170:197-203.
- Weder ND, Aziz R, Wilkins K, Tampi RR. Frontotemporal dementias: a review. *Ann Gen Psychiatry.* 2007;6:15.
- Wongergem R, Pisters MF, Wouters EJ, et al. The course of activities in daily living: who is at risk for decline after first ever stroke?. *Cerebrovasc Dis.* 2017;43:1-8.
- Ekker MS, Boot EM, Singhal AB, et al. epidemiology, aetiology, and management of ischaemic stroke in young adults. *Lancet Neurol.* 2018;17:790-801.
- Rahme R, Moussa R. The modic vertebral endplate and marrow changes: pathologic significance and relation to low back pain and segmental instability of the lumbar spine. *AJNR Am J Neuroradiol.* 2008;29:838-42.
- Ofiram E, Garvey TA, Schwender JD, et al. Cervical degenerative index: a new quantitative radiographic scoring system for cervical spondylosis with interobserver and intraobserver reliability testing. *J Orthop Traumatol.* 2009;10:21-6.
- Mesregah MK, Repajic M, Mgbam P, et al. Trends and patterns of cervical degenerative disc disease: an analysis of magnetic resonance imaging of 1300 symptomatic patients. *Eur Spine J.* 2022;31:2675-83.
- Swanson BT, Creighton D. Cervical disc degeneration: important considerations for the manual therapist. *J Man Manip Ther.* 2022;30:139-53.
- Baldarçara L, Currie S, Hadjivassiliou M, et al. Consensus paper: radiological biomarkers of cerebellar diseases. *Cerebellum.* 2015;14:175-96.
- Duan S, Lv S, Ye F, Lin Q. Imaging anatomy and variation of vertebral artery and bone structure at craniocervical junction. *Eur Spine J.* 2009;18:1102-8.
- Gülsün M, Saatci I, Akata D, et al. Radiologic investigation of vertebrobasilar insufficiency and quantification of vertebrobasilar flow with magnetic resonance imaging. *Tani Girisim Radyol.* 2003;9:279-86.
- Lin SY, Lin CL, Chen DC, et al. Risk of posterior circulation stroke in patients with cervical spondylosis: A nationwide, population-based study. *Atherosclerosis.* 2018;277:42-6.
- Chen CC, Chung CY, Lee TH, et al. Increased risk of posterior circulation infarcts among ischemic stroke patients with cervical spondylosis. *Neuropsychiatr Dis Treat.* 2015;11:273-8.
- Denis DJ, Shedid D, Shehadeh M, et al. Cervical spondylosis: a rare and curable cause of vertebrobasilar insufficiency. *Eur Spine J.* 2014;23:206-13.

24. Vierunen RM, Haapamäki VV, Koivikko MP, Bensch FV. Ankylosis of the cervical spine increases the incidence of blunt cerebrovascular injury (BCVI) in CTA screening after blunt trauma. *Emerg Radiol.* 2022;29:507-17.
25. Lin WS, Huang TF, Chuang TY, et al. Association between cervical spondylosis and migraine: a nationwide retrospective cohort study. *Int J Environ Res Public Health.* 2018;15:587.
26. Okuno S, Touho H, Ohnishi H, Karasawa J. Cervical infarction associated with vertebral artery occlusion due to spondylotic degeneration: case report. *Acta Neurochir (Wien).* 1998;140:981-5.
27. Nishikawa H, Miya F, Kitano Y, et al. Positional occlusion of vertebral artery due to cervical spondylosis as rare cause of wake-up stroke: report of two cases. *World Neurosurg.* 2017;98:877.e13-877.e21.
28. Fleming JB, Vora TK, Harrigan MR. Rare case of bilateral vertebral artery stenosis caused by C4-5 spondylotic changes manifesting with bilateral bow hunter's syndrome. *World Neurosurg.* 2013;79:799.E1-5.
29. Secomb TW. Hemodynamics. *Compr Physiol.* 2016;6:975-1003.
30. Tu YK, Liu HM. Effects of isovolemic hemodilution on hemodynamics, cerebral perfusion, and cerebral vascular reactivity. *Stroke.* 1996;27:441-5.
31. Gomolka RS, Chrzan RM, Urbanik A, et al. Quantification of image contrast of infarcts on computed tomography scans. *Neuroradiol J.* 2017;30:15-22.



Placenta Accreta Spectrum Management and Outcomes: A Comparative Analysis of Syrian Refugees and Turkish Citizens Giving Birth in a Tertiary Hospital

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Abstract

Aim: Placenta accreta spectrum disorders (PAS) are a global threat to maternal well-being. The aim of this study was to assess differences in clinical characteristics and maternal outcomes between Turkish natives and Syrian refugees giving birth with a diagnosis of PAS at a tertiary centre, and to experience the management of this condition in the unique context of Türkiye, home to one of the world's largest refugee populations.

Material and Method: A retrospective study was conducted using the medical records of 228 singleton pregnancies at high risk of PAS, between January 2019 and October 2022. PAS risk assessment was initially performed by ultrasound at mid-trimester, with diagnosis confirmed histologically or clinically, indicating the presence of placental retention following attempted manual removal. The study population was divided into two groups: native and refugee. We investigated disparities in demographic and medical characteristics and primary maternal and neonatal outcomes.

Results: The study found an increased prevalence of previous cesarean delivery ($p=0.005$), anterior placenta ($p<0.000$), placenta previa ($p=0.047$), and deeper placental invasion (increta/percreta) ($p<0.000$) in the native group ($n=161$). The native group had a significantly higher rate of estimated blood loss (2093.5 ± 1516.4 mL vs. 714.1 ± 731.6 mL, $p<0.000$) and peripartum hysterectomy ($p=0.005$) compared to the refugee group ($n=67$). The refugee group had a notably higher incidence of delayed diagnosis ($p<0.000$) and a shorter surgery duration ($p=0.027$) compared to the native group.

Conclusion: The current study highlights significant differences in patient characteristics and outcomes between native and refugee pregnant women with PAS. Despite facing challenges, these women did not encounter adverse perinatal outcomes, indicating the efficacy of healthcare interventions.

Keywords: Disparities, placenta accreta spectrum, Syrian refugees, Turkish natives

INTRODUCTION

Placenta accreta spectrum (PAS) is a histopathological term for the abnormal attachment of all or part of the placenta to the myometrium of the underlying uterine wall (1). This condition is mainly defined by the lack of decidua, leading to the direct attachment of chorionic villi to the myometrial fibers. It is divided into three categories: placenta accreta, placenta increta and placenta percreta, based on the depth of myometrial invasion by the placental villi (2).

In recent decades, the incidence of PAS has been increasing (3,4), closely linked to the global rise in cesarean delivery rates (5). This trend is similarly observed in Türkiye, where the cesarean delivery rate has steadily climbed from 7% in

1993 to 52% in 2018 (6,7). Placenta previa, previous uterine surgery, in vitro fertilization (IVF) and advanced maternal age are other recognised risk factors (8-10).

PAS presents a significant global health challenge due to its association with increased maternal morbidity and mortality. About 60% of affected pregnancies experience severe bleeding, with a mortality rate of up to 7% (11). This often necessitates cesarean hysterectomy and can potentially result in organ damage, sepsis, and disseminated intravascular coagulation (12,13). Prenatal diagnosis plays a crucial role in initiating appropriate management, allowing multidisciplinary planning, and facilitating referral to specialized centers, all of which contribute to a reduction in the risk of maternal mortality and morbidity (14).

CITATION

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Migration has emerged as an unprecedented global phenomenon, becoming an integral facet of life in numerous societies. The management and outcomes of PAS present unique challenges in populations with diverse sociodemographic backgrounds (15). These challenges may be particularly pronounced in the case of refugees, where barriers such as limited access to healthcare services, language differences, cultural distinctions, and socioeconomic factors are often prevalent. In such cases, there may be additional challenges in the early diagnosis of PAS, which is crucial. These difficulties may also be common in the Syrian refugee population living in Türkiye, but it is not possible to definitively determine this because of the limited data available. Therefore, the objective of this study was to assess the incidence, management, and outcomes of PAS among Syrian refugees and Turkish natives.

MATERIAL AND METHOD

A retrospective study was conducted using the medical records of 228 patients with singleton pregnancies at high risk of PAS, who were delivered in the perinatology department of a state tertiary hospital between January 2019 and October 2022.

The study protocol was approved by the Ethics Committee of the University of Health Sciences Etlik Zübeyde Women's Gynecology Training and Research Hospital (2021/99). PAS was primarily diagnosed by mid-trimester ultrasound by a fetal medicine specialist. This involved evaluating sonographic markers using grayscale and color Doppler imaging, as well as adhering to a standardized reporting protocol for sonographic findings. This protocol includes criteria such as loss of the hypoechoic retroplacental clear zone, abnormal placental lacunae, or myometrial thinning as outlined by the European Working Group on Abnormally Invasive Placenta (EW-AIP) (16). Furthermore, the severity of PAS (placenta accreta, placenta increta, and placenta percreta) at delivery was evaluated using the International Federation of Gynaecology and Obstetrics (FIGO) clinical grading system (17) and the International Society of Abnormally Invasive Placenta (IS-AIP) guideline (18). Surgical strategy was standardised, with all patients receiving pre-delivery counselling regarding the need for focal excision or cesarean hysterectomy in cases with evidence of abnormal placental adhesion, regardless of attempts to control bleeding with uterotonics, mechanical intervention or surgical methods. Based on the expected severity of PAS and to optimize perinatal outcomes, patients with PAS were planned for cesarean delivery between 34 and 37 weeks' gestation. Emergency cesarean delivery was performed before 34 weeks' gestation if the patient had severe vaginal bleeding, premature rupture of membranes, or signs of preterm labor indicated by uterine contractions.

Data extracted from hospital medical records included maternal demographic and medical characteristics such as gravidity, parity, history of uterine surgery, number of previous cesarean deliveries, placental location (anterior

or posterior), presence of placenta previa (defined as complete or marginal <2 cm from the cervix) and severity of PAS. Maternal outcomes encompassed factors such as duration of surgery, estimated blood loss (assessed by examination of blood in the aspirator container and sponges), transfusion of blood products, and any surgical or non-surgical interventions performed during delivery. Neonatal outcomes included variables such as gestational age, birth weight, 5-minute Apgar score, and neonatal intensive care unit (NICU) admission.

The analysis was conducted utilizing the Statistical Package, version 28.0 (IBM Corporation, Armonk, New York, USA). The study used mean±(standard deviation) or median±(minimum-maximum) to describe numerical data. Furthermore, parametric variables were analyzed using the Student's t-test, while nonparametric variables were assessed using the Mann-Whitney U test. The chi-square test was employed to evaluate associations among categorical variables, with statistical significance set at a p-value<0.05.

RESULTS

From January 2019 to October 2022, a total of 228 pregnant women diagnosed with PAS were included in the study. The study population consisted of two groups: refugees (n=67, 29.4%) and natives (n=161, 70.6%), all of whom underwent cesarean delivery.

The results of the demographic and medical characteristics that were measured are shown in Table 1. Both groups showed similarity in terms of prior uterine surgery and IVF. The native group had a higher BMI and smoking rate (p<0.000 and p=0.017, respectively), whereas the refugee group had a lower age and higher parity rate, with a significant difference (p<0.000). The native group had significantly higher rates of previous cesarean delivery (p<0.000), placenta previa (p=0.047) and deeper placental invasion (increta/percreta) (36.7% vs. 7.5%, p<0.000). Regarding placental location, the refugee group had a higher rate of posterior placentation (69% vs. 45%, p<0.000) and intrapartum diagnosis (31.3% vs. 8.7%, p<0.000) compared to the native group.

The maternal outcomes are shown in Table 2. The duration of surgery was longer in refugee group (158.3±41.4 min vs. 142.8±32.6 min, p=0.027). The estimated blood loss (2093.5±1516.4 mL vs. 714.1±731.6 mL, p<0.000) and the rate of peripartum hysterectomy were higher in native group (73.2% vs. 47.7%, p=0.005). However, conservative management techniques such as intrauterine balloon tamponade replacement (34.3% vs. 11.2%, p=0.001) and compression sutures (37.3% vs. 11.9%, p=0.001) were used more frequently in the refugee group.

Neonatal outcomes are shown in Table 3. There were no significant differences observed in the 5-minute Apgar scores between the groups. The refugees group had a higher gestational age (35.5±2.2 weeks vs. 34.6±3.2 weeks, p=0.032) and birth weight (2889±449.1 g vs. 2486±458.7 g, p<0.000).

Table 1. Demographic and medical characteristics				
Antepartum characteristics	Group	Native, (n=161)	Refugee, (n=67)	p-value
Maternal age (years), n (%)	<35	75 (46.6)	54 (80.6)	<0.000
	≥35	86 (53.4)	13 (19.4)	
Parity, n (%)	1	14 (8.6)	1(1.4)	<0.000
	2	44 (27.3)	1(1.4)	
	3	62 (38.5)	5 (7.4)	
	≥4	41(25.6)	60 (89.8)	
Number of previous cesarean deliveries, n (%)	0	19 (11.8)	42 (62.6)	<0.000
	1	69 (42.8)	10 (14.9)	
	2	44 (27.3)	4 (5.9)	
	≥3	29 (18.1)	11(16.6)	
Sex, n (%)	Female	99 (61.4)	53 (79.1)	0.001
	Male	62 (38.6)	14 (20.9)	
Smoking, n (%)		21 (13.1)	2 (2.9)	0.017
Previous uterine surgery, n (%)		11 (6.9)	6 (8.9)	0.384
Previous dilatation and curettage of the uterus, n (%)		16 (9.9)	3 (4.5)	0.148
IVF pregnancy, n (%)		3 (1.9)	5 (7.5)	0.684
BMI (kg/m ²), (median±sd)		30.97±5.21	24.4±4.4	<0.000
Delivery type, n (%)	Planned	98 (60.8)	27 (40.3)	<0.000
	Urgency	63 (39.2)	40 (59.7)	
Placenta previa, n (%)		128 (79.6)	45 (67.2)	0.047
Placenta accreta, n (%)		102 (63.4)	62 (92.6)	<0.000
Placenta (increata and percreata), n (%)		59 (36.7)	5 (7.5)	<0.000
Placental localization, n (%)	Anterior	110 (69%)	30 (45%)	<0.000
	Posterior	51 (31%)	37 (55%)	
Intrapartum diagnosis		14 (8.7%)	21 (31.3%)	<0.000
Maternal age, (mean±sd)		36.2±5.3	33±5.6	0.042

BMI: body mass index, IVF: in vitro fertilization

Table 2. Maternal outcomes				
Outcomes		Native, (n=161)	Refugee, (n=67)	p-value
Operating time, minutes (mean±sd)		142.8±32.6	158.3±41.4	0.027
Estimated blood loss, mL (mean±sd)		2093.5±1516.4	714.1±731.6	<0.000
Transfusion of blood products	The number of RBC units, (mean±sd)	3.3±2.8	1.3±1.4	<0.000
	The number of FFP units, (mean±sd)	2.2±2.5	1.2±2	0.032
	The number of platelet units, (mean±sd)	0.4±0.7	0.2±0.6	0.152
	The number of cryoprecipitate units, (mean±sd)	0.2±0.6	0.4±0.7	0.152
Operative management	Cesarean hysterectomy, n (%)	118 (73.2)	32 (47.7)	0.005
	Intrauterine balloon tamponade, n (%)	18 (11.2)	23 (34.3)	0.001
	Internal iliac artery ligation, n (%)	10 (6.2)	4 (5.9)	0.092
	Uterine compression sutures	19 (11.9)	25 (37.3)	0.001
Major maternal morbidity	Bladder injury, n (%)	25 (15.6)	8 (11.9)	0.335
	Urinary tract injury, n (%)	2 (1.3)	7 (10.5)	0.034
	Vascular injury, n (%)	8 (4.9)	7 (10.5)	0.072
	The wound infection, n (%)	6 (3.8)	3 (4.5)	0.685
	Reoperation, n (%)	5 (3.2)	3 (4.5)	0.838
	Thromboemboly, n (%)	4 (2.5)	4 (5.9)	0.551
	Bowel injury, n (%)	0	1 (1.5)	0.167
	Postop.hemorrhage, n (%)	6 (3.8)	2 (2.9)	0.2450
	Sepsis, n (%)	0	1 (1.5)	0.167
	The intensive care unit admission, n (%)	48 (29.9)	16 (23.9)	0.318

RBC: red blood cell, FFP: fresh frozen plasma

Table 3. Neonatal outcomes

Outcomes	Native, (n=161)	Refugee, (n=67)	p-value
Gestational age, weeks (mean±sd)	34.6±3.2	35.5±2.2	0.032
Apgar score at 5 min, (mean±sd)	7.4±0.9	7.6±0.7	0.159
Birth weight,g (mean±sd)	2486±458.7	2889±449.1	<0.000
NICU, n (%)	61 (39.2)	41 (61.2)	0.004

NICU: neonatal intensive care unit

DISCUSSION

The Syrian refugee crisis has led to a large influx of refugees seeking safety and protection in neighboring countries such as Türkiye. Türkiye is home to the largest number of Syrian refugees worldwide, with 3,713,344 people officially registered, 18.2% of whom are women aged 18 and over (19). The growing number of refugees worldwide poses particular challenges to providing adequate healthcare, especially for pregnant women. Previous studies have extensively documented significant inequalities in maternal morbidity and mortality, highlighting the disproportionate impact on minority populations based on race and ethnicity (20-23). However, studies of health inequalities emphasize that the effects of race and ethnicity are due to social structures rather than biological or genetic differences (24-26). Understanding social determinants of health is crucial as they encompass the circumstances in which individuals are born, raised, reside, labor, and age. These factors also include socioeconomic status, education, employment, housing, and access to healthcare (27,28). This may be particularly evident in the context of Syrian refugees living in Türkiye, where language barriers, cultural differences and socioeconomic factors may lead to disparities in access to healthcare services (28).

Recent research has shown that a significant proportion of pregnant Syrian refugees receive inadequate antenatal care compared to the non-refugee population (29). However, the results of a study conducted in Lebanon are different, possibly because of the presence of Arabic as a spoken language, which facilitates communication for Arabic-speaking Syrian refugees. Interestingly, the same study found that antenatal follow-up rates among pregnant women in Syria before the war were significantly higher than those in Lebanon (29). This demonstrates the influential role of language while recognizing that other factors influence access to appropriate health services. These challenges may result in delayed or inadequate antenatal care, thereby limiting the early diagnosis and management of PAS. In Addition, multiple studies have consistently shown that planned delivery, in contrast to emergency delivery, is significantly associated with reduced blood transfusion requirements and improved neonatal outcomes in cases of PAS (30-33).

Natives are generally more familiar with the healthcare system and have better access to prenatal care, which may facilitate earlier diagnosis and appropriate management of PAS. Nevertheless, it was important to critically assess whether Turkish pregnant women with PAS were really more

fortunate than Syrian pregnant women because several known factors were associated with an increased risk of PAS in Turkish women. A meta-analysis examining the total number of cesarean deliveries among Syrian refugees in Türkiye revealed a significantly lower rate compared with the Turkish population (34). In particular, previous research has consistently identified a previous caesarean delivery as the most important risk factor for the development of PAS (35,36). Crucially, the incidence of PAS increases with the number of previous cesarean deliveries, from about 0.3% in women with one cesarean delivery to about 7% in those with more than five (35). This study found that the rate of cesarean section was significantly higher among Turkish pregnant women compared to Syrian pregnant women ($p<0.000$).

Placenta previa is another significant and independent risk factor for the development of PAS (36). Previous studies have consistently shown that when placenta previa with PAS is located in the anterior uterine wall, there's an increased risk of postpartum hemorrhage, often necessitating massive transfusions and potentially resulting in hysterectomy (37). The current study found a higher prevalence of specific risk factors for maternal morbidity among Turkish women, including higher incidence of anterior placenta ($p<0.000$), placenta previa ($p=0.047$) and peripartum hysterectomy ($p=0.005$) compared to Syrian women.

A previous study showed that placenta percreta was associated with increased maternal morbidity despite planned management and the application of additional measures, typically used in cases of PAS (37). This study found that Turkish women had higher incidence of deeper placental invasion (increta/percreta) ($p<0.000$) and estimated blood loss ($p<0.000$) during delivery. In line with Morgan's research (38), posterior placenta ($p<0.000$), delayed diagnosis ($p<0.000$) and the use of conservative management approaches (e.g., intrauterine balloon tamponade replacement, uterine compression sutures, and internal iliac artery ligation) ($p=0.001$) were found significantly more common among Syrian pregnant women, who also had lower rates of previous cesarean deliveries. Similar to our findings, previous research has suggested that PAS cases with a posterior placental position were less likely to present as increta or percreta, conditions associated with increased maternal morbidity (36-38). This is probably the main reason that the Syrian pregnant women in our study had better maternal and surgical outcomes than the Turkish pregnant women, despite lower rates of prenatal follow-up and delayed diagnosis.

While acknowledging the limitations of the retrospective study and the need for cautious interpretation of the results, it is important to highlight that the study represents the first investigation of obstetric data and outcomes among Syrian refugees with PAS in Türkiye. Despite the challenges they faced in accessing antenatal care and language problems, the refugee pregnant women in our study did not experience adverse perinatal outcomes.

CONCLUSION

Given the potentially life-threatening nature of PAS disorders, it is essential to further investigate the differences between local and refugee pregnant populations to optimize adverse maternal and neonatal outcomes.

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REFERENCES

1. Usta IM, Hobeika EM, Musa AA, et al. Placenta previa-accreta: risk factors and complications. *Am J Obstet Gynecol.* 2005;193:1045-9.
2. Luke RK, Sharpe JW, Greene RR. Placenta accreta: the adherent or invasive placenta. *Am J Obstet Gynecol.* 1966;95:660-8.
3. Silver RM, Branch DW. Placenta accreta spectrum. *N Engl J Med.* 2018;378:1529-36.
4. Creanga AA, Bateman BT, Butwick AJ, et al. Morbidity associated with cesarean delivery in the united states: is placenta accreta an increasingly important contributor?. *Obstetric Anesthesia Digest.* 2016;36:138.
5. Eshkoli T, Weintraub AY, Sergienko R, Sheiner E. Placenta accreta: risk factors, perinatal outcomes, and consequences for subsequent births. *Obstetric Anesthesia Digest.* 2014;34:19-20.
6. Hacettepe University Institute of Population Studies. 2018 Turkey Demographic and Health Survey. Ankara, Turkey, HUIPS, 2019.
7. Eyi EGY, Mollamahmutoglu L. An analysis of the high cesarean section rates in Turkey by Robson classification. *J Matern Fetal Neonatal Med.* 2021;34:2682-92.
8. Baldwin HJ, Patterson JA, Nippita TA, et al. Antecedents of abnormally invasive placenta in primiparous women: risk associated with gynecologic procedures. *Obstet Gynecol.* 2018;131:227-33.
9. Fitzpatrick KE, Sellers S, Spark P, et al. Incidence and risk factors for placenta accreta/increta/percreta in the UK: a national case-control study. *PLoS One.* 2012;7:e52893.
10. Piñas Carrillo A, Chandraharan E. Placenta accreta spectrum: Risk factors, diagnosis and management with special reference to the Triple P procedure. *Women's Health.* 2019;15:1745506519878081.
11. O'Brien JM, Barton JR, Donaldson ES. The management of placenta percreta: conservative and operative strategies. *Am J Obstet Gynecol.* 1996;175:1632-8.
12. D'Antonio F, Iacovella C, Bhide A. Prenatal identification of invasive placentation using ultrasound: systematic review and meta-analysis. *Ultrasound Obstet Gynecol.* 2013;42:509-17.
13. Buca D, Liberati M, Cali G, et al. Influence of prenatal diagnosis of abnormally invasive placenta on maternal outcome: systematic review and meta-analysis. *Ultrasound Obstet Gynecol.* 2018;52:304-9.
14. Nieto Calvache AJ, Hidalgo A, López MC, et al. Placenta accreta spectrum in vulnerable population: how to provide care for pregnant refugees struggling to access affordable healthcare. *J Matern Fetal Neonatal Med.* 2022;35:5031-4.
15. McCall SJ, El Khoury TC, Ghattas H, et al. Maternal and infant outcomes of Syrian and Palestinian refugees, Lebanese and migrant women giving birth in a tertiary public hospital in Lebanon: a secondary analysis of an obstetric database. *BMJ Open.* 2023;13:e064859.
16. Collins SL, Ashcroft A, Braun T, et al. Proposal for standardized ultrasound descriptors of abnormally invasive placenta (AIP). *Ultrasound Obstet Gynecol.* 2016;47:271-5.
17. Jauniaux E, Ayres-de-Campos D, Langhoff-Roos J, et al. FIGO classification for the clinical diagnosis of placenta accreta spectrum disorders. *Int J Gynaecol Obstet.* 2019;146:20-4.
18. Collins SL, Alemdar B, van Beekhuizen HJ, et al. Evidence-based guidelines for the management of abnormally invasive placenta: recommendations from the International Society for Abnormally Invasive Placenta. *Am J Obstet Gynecol.* 2019;220:511-26.
19. Directorate General for Migration Management (2019) Temporary protection in European Union. Ministry Interior of Turkey, Directorate General for Migration Management. <https://en.goc.gov.tr/temporary-protection-in-european-union> access date 5.02.2020.
20. Bryant AS, Worjolah A, Caughey AB, Washington AE. Racial/ethnic disparities in obstetric outcomes and care: prevalence and determinants. *Am J Obstet Gynecol.* 2010;202:335-43.
21. Bryant A, Mhyre JM, Leffert LR, et al. The association of maternal race and ethnicity and the risk of postpartum hemorrhage. *Anesth Analg.* 2012;115:1127-36.
22. Admon LK, Winkelman TN, Zivin K, et al. Racial and ethnic disparities in the incidence of severe maternal morbidity in the United States, 2012–2015. *Obstet Gynecol.* 2018;132:1158-66.
23. Williams DR, Sternthal M. Understanding racial-ethnic disparities in health: sociological contributions. *J Health Soc Behav.* 2010;51:S15-27.
24. Kirby JB, Taliaferro G, Zuvekas SH. Explaining racial and ethnic disparities in health care. *Med Care.* 2006;44:164-72.

25. Egede LE. Race, ethnicity, culture, and disparities in health care. *J Gen Intern Med.* 2006;21:667-9.
26. Thomas PE, Beckmann M, Gibbons K. The effect of cultural and linguistic diversity on pregnancy outcome. *Aust N Z J Obstet Gynaecol.* 2010;50:419-22.
27. McKeary M, Newbold B. Barriers to care: the challenges for Canadian refugees and their health care providers. *J Refug Stud.* 2010;23:523-45.
28. Erenel H, Aydogan Mathyk B, Sal V, et al. Clinical characteristics and pregnancy outcomes of Syrian refugees: a case-control study in a tertiary care hospital in Istanbul, Turkey. *Arch Gynecol Obstet.* 2017;295:45-50.
29. Benage M, Greenough PG, Vinck P, et al. An assessment of antenatal care among Syrian refugees in Lebanon. *Confl Health.* 2015;9:8.
30. Shamshirsaz AA, Fox KA, Salmanian B, et al. Maternal morbidity in patients with morbidly adherent placenta treated with and without a standardized multidisciplinary approach. *Obstetric Anesthesia Digest.* 2016;36:31-2.
31. Shamshirsaz AA, Fox KA, Erfani H, et al. Outcomes of planned compared with urgent deliveries using a multidisciplinary team approach for morbidly adherent placenta. *Obstet Gynecol.* 2018;131:234-41.
32. Thang NM, Anh NTH, Thanh PH, et al. Emergent versus planned delivery in patients with placenta accreta spectrum disorders: a retrospective study. *Medicine (Baltimore).* 2021;100:e28353.
33. Senoglu A, Ozturk M, Karacam Z. Cesarean section rates and indications in Turkey: a systematic review and meta-analysis. *Asian J Res Nur Health.* 2021;4:31-57.
34. Carusi DA. The placenta accreta spectrum: epidemiology and risk factors. *Clin Obstet Gynecol.* 2018;61:733-42.
35. Bowman ZS, Eller AG, Bardsley TR, et al. Risk factors for placenta accreta: a large prospective cohort. *Am J Perinatol.* 2014;31:799-804.
36. Matsubara S, Baba Y, Takahashi H. Placenta previa and hemorrhage: the placental location may be an important determinant of the bleeding amount. *J Matern Fetal Neonatal Med.* 2018;31:1390-1.
37. Marcellin L, Delorme P, Bonnet M, et al. Placenta percreta is associated with more frequent severe maternal morbidity than placenta accreta. *Obstetric Anesthesia Digest.* 2019;39:94-6.
38. Morgan EA, Sidebottom A, Vacquier M, et al. The effect of placental location in cases of placenta accreta spectrum. *Am J Obstet Gynecol.* 2019;221:357.e1-5.



Evaluation of Knowledge, Attitudes and Behaviors of Physicians Working in a University Hospital About Smoking Cessation Treatment

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Abstract

Aim: Tobacco use is a preventable cause of morbidity and mortality and a global public health problem. It is clear that physicians need to increase their awareness, increase their level of knowledge, and change their negative attitudes and behaviours about smoking, which is a risk factor for many preventable diseases in the world. This study was planned to evaluate the knowledge, attitudes and behaviours of physicians working in a university hospital regarding smoking cessation treatments.

Material and Method: This study was a descriptive and cross-sectional study. The study included 203 physicians. A printed questionnaire form was used to collect data. Nicotine dependence of the participants who smoked cigarettes was evaluated by Fagerström nicotine dependence test (FNBT). Data were analyzed using SPSS 23.0 statistical package form. A value of $p < 0.05$ was accepted for statistical significance.

Results: The mean number of correct answers given by the participants to a total of 20 questions measuring the level of knowledge about smoking cessation counselling was 13.41 ± 3.80 . Among the physicians, 14.3% ($n=29$) had received smoking cessation counselling training and 85.7% ($n=174$) had not received any training. When the knowledge scores of the participants were analyzed according to the status of receiving smoking cessation counselling training, it was seen that the mean correct answers given to the knowledge questions by the participants who received training were significantly higher ($p=0.023$).

Conclusion: In addition to receiving smoking cessation counselling training, participants' having more time spent in medical education, such as being a specialist and lecturer, was found to be associated with higher awareness of smoking and more positive attitudes and behaviours regarding smoking cessation treatments. Increasing the number and quality of trainings related to smoking and smoking cessation counselling will make significant contributions to the awareness, knowledge, attitudes and behaviours of physicians on this issue.

Keywords: Smoking, smoking cessation, physicians

INTRODUCTION

Tobacco usage stands as a pivotal risk element for chronic non-communicable ailments and is a preventable contributor to morbidity and mortality (1). Its pervasive influence is felt globally, with smoking and addiction having claimed the lives of approximately 100 million individuals in the 20th century, and a projected toll of 1 billion in the 21st century. Smoking significantly escalates the risk for various ailments like cardiovascular diseases, cancer, chronic respiratory conditions, and diabetes, which collectively stand as leading causes of global mortality (2).

According to the World Health Organization (WHO), over 1.1 billion people were tobacco users in 2015, accounting

for 15% of the world's populace. Annually, nearly 7 million individuals succumb to smoking or tobacco-related usage, including passive exposure. This figure is anticipated to rise to 8.5 million by 2030 (1). Notably, China, Indonesia, and India rank highest in tobacco prevalence globally, with Türkiye featuring as the tenth country with approximately 18 million tobacco users. The combined consumption within these top 10 nations, including Türkiye, constitutes two-thirds of global tobacco usage (3).

In Türkiye, 19.2 million individuals (31.6%) smoke cigarettes or other tobacco products, with a smoking rate of 44.1% among men and 19.2% among women. On average, smokers consume 18 cigarettes daily, with approximately 15% initiating smoking before the age of 15. Among those

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who began smoking before 18, the average initiation age stands at 17 (4).

Physicians and healthcare professionals bear significant duties in disease prevention and health enhancement. A simple yet effective approach within tobacco control entails inquiring about smoking status and advising cessation to patients. Studies indicate that physicians can achieve 5-10% smoking cessation rates through such interventions alone (5,6).

Beyond serving as role models for a smoke-free lifestyle, physicians play a crucial role in combating smoking by questioning patients about their smoking habits, advising cessation, and providing information and guidance on appropriate cessation methods. Research underscores the need to elevate physicians' awareness and knowledge regarding smoking, particularly among primary care providers who cater to diverse health needs within society. It is imperative for physicians to enhance their awareness, knowledge, and attitudes towards smoking, a modifiable risk factor for numerous preventable diseases worldwide. Especially in primary care medicine, there is a need for a community-oriented but also patient-centred and long-term medical approach that focuses on addiction and supports a healthy lifestyle at a time of serious health problems. This study was planned to evaluate the knowledge, attitudes and behaviors of physicians working in a university hospital regarding smoking cessation treatments.

MATERIAL AND METHOD

This study is a descriptive and cross-sectional study. The study included 203 physicians who agreed to participate. A printed questionnaire form was used to collect data. This questionnaire was based on the literature. The questionnaire form was delivered to all participants by hand.

The questionnaire was determined by reviewing similar previous studies and finalized by pre-application in a small group of residents, specialists and faculty members before starting our study. In the questionnaire, questions were asked to measure the sociodemographic characteristics of the participants, smoking status, smoking cessation counseling training, awareness of the smoking cessation outpatient clinic in our hospital, attitudes of physicians towards patients in smoking cessation treatment, and behaviors related to smoking addiction and smoking cessation treatments. In addition, the Fagerström nicotine dependence test consisting of 6 questions was administered to measure the addiction level of physicians who smoked. The Turkish validity of the Fagerström nicotine dependence test was studied by Uysal et al. and found to be moderately reliable (7). The Fagerström nicotine dependence test (FNBT) consists of 6 questions and points are given according to the answers given to the questions. Maximum score is 10 and minimum score is 0. 0-2 points: Very little dependent; 3-4 points: Slightly dependent; 5 points: Moderately dependent; 6-7 points: Highly dependent; 8-10 points: Very highly dependent.

Sample Size Analyses

When the studies were analysed, a power analysis was

performed by taking into account the knowledge of smoking cessation treatments, which is one of the main results of the study. In the sample calculation using Russ Lenth's Java applet (Piface), a similar study was taken into consideration and the sample size was calculated taking into account Type I error (0.05), targeted power (0.80) and it was concluded that there should be at least 196 people. However, 203 people were reached in total.

Statistical Analysis

In the descriptive statistics of the study, numerical data were expressed as mean and standard deviation or median (minimum-maximum) according to normality. Categorical data were expressed as number and percentage. The distribution of numerical data was analyzed by Kolmogorov-Smirnov Z Test and histogram graphs. Numerical data in two groups were analyzed by Student's t test. Numerical data between more than two independent groups were analyzed by One Way Anova and Kruskal Wallis tests. Tamhane test was used for post hoc analysis. Chi-Square test was used to analyze categorical variables. P significance value was accepted as <0.05. SPSS 23.0 package program was used in the analyses.

Ethical Aspects of the Research

The ethics committee approval of this study was obtained with the decision number 2022/209 dated 05.12.2022 and numbered 2022/209 of Düzce University Non-Interventional Health Research Ethics Committee.

RESULTS

A total of 203 physicians took part in the study. Among them, 47.8% (n=97) were female, while 52.2% (n=106) were male. Regarding marital status, 49.8% (n=101) were married, and 50.2% (n=102) were single.

Analyzing the general branches of the participants, 4.9% (n=10) were in preclinical fields, 68.5% (n=139) were internal medicine specialists, and 26.6% (n=54) were surgical physicians.

In terms of professional roles, 80.8% (n=164) were research assistants, 2% (n=4) were specialists, and 17.2% (n=35) were faculty members (Table 1).

	n	%	
Gender	Female	97	47.8
	Male	106	52.2
Marital status	Married	101	49.8
	Single	102	50.2
General branch	Preclinical medicine	10	4.9
	Internal medicine	139	68.5
	Surgical medicine	54	26.6
Title	Research assistant	164	80.8
	Specialist	4	2.0
	Academic staff	35	17.2

The mean age of the participants was 31.34±6.87 (minimum=24, maximum=61). There was a significant

difference between age and smoking status of physicians ($p=0.002$). It was observed that those who had never smoked had a lower mean age. Post-hoc analysis showed no significant age difference between the groups ($p>0.05$). The median duration of the participants' medical practice was 6.50 (minimum=0.5, maximum=37) years. A significant difference was observed between the duration of the participants' medical practice and their smoking

status ($p=0.007$). Physicians who had never smoked were found to have a lower mean duration of practice. The mean number of correct answers given by the participants to a total of 20 questions measuring the level of knowledge about smoking cessation counseling was 13.41 ± 3.80 (minimum=1, maximum=20). There was no statistically significant difference between the knowledge scores of the participants and their smoking status ($p>0.05$) (Table 2).

Table 2. Smoking status of participants according to age, number of children, length of practice and knowledge scores

	Total (n=203)	Smoking status			p
		Using (n=32)	Quit (n=17)	Never drank (n=154)	
		Mean±SD	Mean±SD	Mean±SD	
Age	31.34±6.87	32.53±6.74	34.06±8.30	30.79±6.68	0.002
Duration of residency	6.69±6.73	8.13±6.74	8.94±8.76	6.15±6.43	0.007
Number of correctly answered knowledge questions	13.41±3.80	13.44±3.22	15.24±3.27	13.20±3.93	0.095

In order to measure the awareness of the physicians who participated in our study about smoking cessation outpatient clinic, their knowledge about the existence of smoking cessation outpatient clinic and their patient referral status were questioned. 78.8% (n=160) of the participants answered the question "Is there a smoking cessation outpatient clinic in the institution where you work?", 0.5% (n=1) answered yes, 0.5% (n=1) answered no, and 20.7% (n=42) answered don't know. To the question "Have you ever referred a patient to a smoking cessation outpatient clinic?" 50.2% (n=102) of the physicians answered yes, 49.8% (n=101) answered no.

Participants were queried regarding their receipt of smoking cessation counseling training and the sources thereof. Results indicated that 14.3% (n=29) of physicians had undergone such training, while the majority, comprising 85.7% (n=174), had not.

Among the 29 physicians who had received training, the breakdown of training sources was as follows: 7 individuals reported exclusive training from the Ministry of Health, 12 from their respective universities, 1 solely from specialty training, 3 exclusively from attendance at

congresses, 1 from other institutions exclusively, 1 from both the Ministry of Health and congresses, 2 from both the Ministry of Health and their universities, 1 from both the Ministry of Health, their university, and congresses, and 1 from a combination of their university, specialty training, and congresses.

When the FNBT scores of the participants who smoked cigarettes were evaluated, it was determined that 41.9% (n=13) were very low, 25.8% (n=8) were low, 12.9% (n=4) were moderate, 12.9% (n=4) were high and 6.5% (n=2) were very high nicotine addicted.

When the smoking status of the participants was analyzed according to their gender, a significant difference was observed ($p=0.004$). It was observed that the rate of smoking was lower in female physicians compared to male physicians. A significant difference was observed between the marital status of the participants and their smoking status ($p=0.002$). It was observed that married participants had higher smoking rates than single participants. There was no significant difference between the presence of children, general branch and title of the participants and smoking status ($p>0.05$) (Table 3).

Table 3. Smoking status of participants according to gender, marital status, presence of children, general branch and title

		Smoking status			p
		Using	Quit	Never drank	
		n (%)	n (%)	n (%)	
Gender	Female	7 (21.88)	7 (41.18)	83 (53.90)	0.004
	Male	25 (78.13)	10 (58.82)	71 (46.10)	
Marital status	Married	23 (71.88)	12 (70.59)	66 (42.86)	0.002
	Single	9 (28.13)	5 (29.41)	88 (57.14)	
Child presence	Yes	11 (34.38)	6 (35.29)	45 (29.22)	0.767
	No	21 (65.63)	11 (64.71)	109 (70.78)	
General branch	Preclinical medicine	1 (3.13)	0 (0.00)	9 (5.84)	0.791
	Internal medicine	23 (71.88)	13 (76.47)	103 (66.88)	
	Surgical medicine	8 (25.00)	4 (23.53)	42 (27.27)	
Title	Research assistant	26 (81.25)	14 (82.35)	124 (80.52)	0.961
	Specialist	1 (3.13)	0 (0.00)	3 (1.95)	
	Academic staff	5 (15.63)	3 (17.65)	27 (17.53)	

When the knowledge scores of the participants were examined according to their general branches, no significant statistical difference was observed between the variables ($p=0.092$). When the knowledge scores of the participants were analyzed according to their titles, a statistically significant difference was found ($p=0.028$). It was observed that the mean knowledge score of the participants who were research assistants was higher than the mean knowledge score of the participants who were specialists or faculty members (since the number

of specialist physicians was low, the numbers of faculty members and specialist physicians were combined). When the knowledge scores of the participants were examined according to their smoking cessation counseling training status, a statistically significant difference was observed ($p=0.023$). It was determined that the mean knowledge scores of the participants who received smoking cessation counseling training were higher than those of the participants who did not receive training (Table 4).

Table 4. Knowledge scores of participants according to their titles

Title		Number of correctly answered knowledge questions			
		n	Mean	SD	p
Research assistant	Research assistant	164	13.70	3.37	0.028
	Specialist+academic staff*	39	12.21	5.11	
Smoking cessation counseling training	Yes	29	14.90	3.792	0.023
	No	174	13.16	3.760	

*Statistical analysis was performed by combining the number of specialists and faculty members.

In terms of behavioral assessment, the majority of the participants answered "sometimes" for the statement "I ask all my patients who smoke whether they want to quit smoking". In addition, no significant correlation was found between the branches of physicians and their behaviors of questioning their patients whether they smoke or not and advising smoking patients to quit smoking ($p>0.05$).

Propositions were presented to assess the knowledge level of the participants. Participants were asked to mark one of the options of true, false or no idea for each proposition. With 97.5% ($n=173$) of the physicians answering correctly to the proposition "The combination of behavioral therapy methods and pharmacotherapy increases the success of

smoking cessation treatment", this was the proposition with the highest level of knowledge. The statement "For the statement "Smoking cessation treatment should be continued for at least one year", only 9.4% ($n=19$) of the physicians chose the "incorrect" option and 59.6% ($n=121$) chose the "correct" option. Thus, this statement was both the least correct and the most incorrect statement." For the statement "Nicotine replacement therapy (NRT) can be used for smoking cessation in pregnant and breastfeeding women", 49.3% ($n=100$) of the participants responded that they had no idea. This statement was the statement about which the participants had the least opinion. The knowledge level assessment questions and the answers given by the participants are shown in Table 5.

Table 5. Level of knowledge about smoking cessation treatment assessment questions and distribution of answers

Knowledge level	Right n (%)	Wrong n (%)	No opinion n (%)
Motivational talks and cognitive behavioral therapy methods alone are not effective in smoking cessation	73 (36.0)	118 (58.1)*	12 (5.9)
NRT, Varenicline and Bupropion are the primary pharmacotherapies for smoking cessation	173 (85.2)*	9 (4.4)	21 (10.3)
Vaping is a type of treatment within NRT	25 (12.3)	138 (68.0)*	40 (19.7)
The combination of behavioral therapy methods and pharmacotherapy increases the success of smoking cessation treatment	198 (97.5)*	0 (0)	5 (2.5)
Smoking cessation treatment should be continued for at least one year	121 (59.6)	19 (9.4)*	63 (31.0)
NRT, is administered to patients with low nicotine dependence levels	56 (27.6)	98 (48.3)*	49 (24.1)
In order for a person to be considered to have quit smoking, he/she must not have smoked any cigarettes in the last 6 months	114 (56.2)*	26 (12.8)	63 (31.0)
NRT, is safer in terms of side effects than Bupropion and Varenicline	102 (50.2)*	23 (11.3)	78 (38.4)
Nicotine patch and gum are nicotine replacement therapy methods used in smoking cessation treatment	185 (91.1)*	1 (0.5)	17 (8.4)
Patients may continue to smoke during nicotine replacement therapy	23 (11.3)	137 (67.5)*	43 (21.2)
The most common side effects in people taking bupropion are headache, insomnia and dry mouth	137 (67.5)*	3 (1.5)	63 (31.0)
Varenicline; As a partial agonist, it stimulates alpha-4 beta-2 nicotinic receptors and reduces nicotine withdrawal symptoms	111 (54.7)*	4 (2.0)	88 (43.3)
NRT, can be used for smoking cessation in pregnant and breastfeeding women	25 (12.3)	78 (38.4)*	100 (49.3)

*The answers that must be marked in order to be considered correctly answered are shown in bold font.

DISCUSSION

In this study, conducted to assess the knowledge, attitudes, and practices of physicians regarding smoking cessation treatments within a university hospital setting, findings revealed a notably low prevalence of smoking among physicians, alongside a correspondingly low level of nicotine addiction among those who did smoke. Furthermore, a striking observation emerged: a minority of physicians reported having received formal training in smoking cessation counseling.

Notably, male physicians and those of advanced age exhibited higher rates of smoking, indicating potential demographic associations with tobacco use among medical professionals. Moreover, a noteworthy disparity in knowledge levels surfaced between physicians who underwent formal smoking cessation counseling training and those who did not. Those who received such training demonstrated a superior grasp of pertinent concepts and practices associated with smoking cessation interventions.

When we look at other studies evaluating smoking rates among physicians, differences between countries are striking. In some studies conducted among physicians, smoking rates were 2.6% in the UK (8), 3% in the USA (9), 7.2% in Brazil (10), 9.6% in Germany (11), 2.9% in women and 12.5% in men in Japan (12), 15.2% in China (13), 18.9% in Portugal (14), 19.2% in Italy (15), 26% in France (16) and 29% in Pakistan (17). In Türkiye, the prevalence of smoking among physicians was found to be between 32.6-66.2% in 22 studies (18-21). The smoking rates of the physicians who participated in our study were found to be higher than the rates obtained in the UK, USA, Brazil, Germany, Japan and China, but lower than the smoking rates in studies conducted in Portugal, Italy, France, Pakistan and Türkiye. This may be explained by the gradual decrease in smoking in our country as well as in the world, especially among physicians.

In our investigation, the degree of nicotine addiction among cigarette-smoking participants was assessed using the FNBT, revealing predominantly low levels of addiction. Upon review of existing literature, it became apparent that physicians, as a cohort, typically exhibit low levels of nicotine dependence. This aligns with findings from our study, where addiction rates were comparable to or even lower than those reported in the literature (22-26).

The observed consistency or even diminution of addiction rates among physicians in our study compared to existing literature is an encouraging indication. It underscores the potential for successful smoking cessation interventions among medical practitioners, promising advancements in tobacco control efforts within this professional demographic.

In our study, it was observed that physicians did not give adequate appropriate answers to the questions questioning their smoking cessation advice to their smoking patients. In the literature, the rates of smoking cessation advice to smoking patients vary significantly (10,18,26,27). The reason for this variability may be that

the level of knowledge of physicians, especially about pharmacological treatments, increases according to their level of training in smoking cessation counseling, and this increased level of knowledge may be thought to trigger the behavior of advising and guiding smoking patients. It is clear that smoking cessation counseling trainings to be organized will positively affect this advice and referral behavior.

A significant difference was observed between the ages of the physicians participating in this study and their smoking status. While the mean age of physicians who never smoked was the lowest, the mean age of physicians who quit smoking was the highest. The mean age of the physicians who smoked was 32.53 ± 6.74 . Similarly, although there are studies in the literature showing that smoking decreases as the average age decreases, there are also studies showing that there is no significant relationship between age and smoking status (26,28,29). The fact that awareness about the harms of smoking and personal health concerns increase with age may explain the emergence of smoking cessation behavior at older ages. At the same time, it may be thought that young physicians are more conscious about smoking and use cigarettes less frequently with the effect of successful tobacco policies in recent years.

In our study, a significant relationship was found between length of practice and smoking status. The duration of practice of the participants who never smoked was found to be significantly lower than the duration of practice of the participants who smoked and quit smoking. In Çerçi's study, similar to our results, the rate of smoking was found to be lower in participants with lower average years of practice (26).

In our study, no statistically significant relationship was found between the number of correctly answered information questions and smoking status. In this regard, our study yielded similar results with previous thesis studies. It is thought-provoking that although the knowledge levels of physicians who smoke about smoking and smoking cessation treatments were similar to those of non-smokers, they continued to smoke. However, the fact that the knowledge levels did not show a significant change may be interpreted as the fact that some of the physicians fulfill the requirements of their profession by not giving place to lack of knowledge on this subject despite smoking.

In our study, men had significantly higher smoking levels than women. According to the Global Adult Tobacco Survey (GATS) 2016 data, the smoking rate of men was 44.1%, while the smoking rate of women was 19.2% (30). The smoking levels of male and female physicians in our study were measured to be lower than the data from Türkiye. Similar to our study, many studies in the literature show that the smoking level of men is higher (12,18,22,23,31).

In our study, the smoking rates of married physicians were statistically significantly higher than the smoking rates of single physicians. In the majority of studies that investigated this relationship, no relationship was found

between marital status and smoking (26,28,29,31). Our study differs from most of the literature in this regard. In our study, the mean age of non-smokers was significantly lower. Considering that the mean age of single physicians may be lower than that of married physicians, the higher rate of smoking among married physicians is an understandable result.

In this study, no significant difference was observed between the smoking status of physicians and their branches. In previous studies, physicians working in surgical departments were found to smoke at a higher rate than those working in internal and basic medicine departments (25,31,32). Although there was no significant difference between department and smoking in our study, when other studies in the literature are considered, it can be said that the department in which physicians work is a factor affecting their smoking status. The fact that the majority of the physicians participating in our study (139/203) were internal medicine physicians may have caused this discrepancy.

In our study, no significant relationship was found between these variables when the smoking status of the participants was examined according to their smoking cessation counseling training status. In Çerçi's study, although the smoking rates of physicians who received smoking cessation counseling training were found to be lower than those of physicians who did not receive training, statistical significance was not found (26). The fact that physicians who do not smoke may have a higher interest in smoking cessation counseling training may explain the lower smoking rates of physicians who received training, although there was no statistical significance.

In our study, a significant difference was found between the titles of the participants and their level of knowledge about smoking cessation counseling. The average of the information questions answered correctly by resident physicians was found to be higher than that of specialists and lecturers. It can be said that the fact that the participation in our study was mostly made by resident physicians and that the majority of these residents were family medicine residents who were actively working in the smoking cessation outpatient clinic of our hospital led to this result.

In our study, it was determined that the mean knowledge scores of the participants who received smoking cessation counseling training were higher than the participants who did not receive training, as expected. In the study conducted by Keten et al. with family physicians in 2014, no significant difference was found in terms of knowledge level between physicians who received and did not receive training on smoking cessation treatments (27). In the thesis study conducted by Çerçi in 2017, the average of correct answers given by physicians who received tobacco addiction training to information questions about smoking cessation treatments was found to be significantly higher compared to physicians who did not receive training (26). When the studies in the literature on this subject are examined, it can be concluded that the contribution of

education to the level of knowledge has increased over the years. One of the factors affecting this result may be thought to be the increase in the quality and accessibility of smoking cessation counseling training.

In our study, a significant difference was found when the number of correct answers given by physicians to the knowledge level questions was compared with their attitudes and behaviors in questioning the smoking status of patients and advising them to quit smoking. This robust association strongly underscores the premise that the primary impediment to the adoption of attitudes and behaviors conducive to smoking cessation among physicians is a deficiency in knowledge. Consequently, the provision of smoking cessation counseling training to medical professionals is posited to exert a beneficial impact not only on knowledge acquisition but also on the cultivation of more favorable attitudes and behaviors toward smoking cessation interventions.

CONCLUSION

The observable decline in smoking rates among young physicians is attributed, in significant part, to the recent implementation of tobacco control policies in our country. This trend is particularly noteworthy given the pivotal role that physicians play as societal role models. Moreover, factors such as receipt of smoking cessation counseling training and extended duration of medical education, including attainment of specialist and lecturer status, were identified as correlates of heightened awareness and more favorable attitudes and behaviors toward smoking cessation interventions.

Enhancing the quantity and quality of training initiatives focused on smoking and smoking cessation counseling, both within medical school curricula and throughout post-graduate education, holds considerable promise for bolstering physicians' awareness, knowledge, attitudes, and practices regarding this critical public health issue. Such endeavors are poised to yield substantial contributions toward the advancement of tobacco control efforts within the medical community.

All physicians, particularly family practitioners entrusted with the provision of preventive healthcare services to the entire community, must heighten their awareness and assume a more proactive stance regarding smoking and tobacco addiction. Given its status as one of the most significant public health challenges of our time, with potential health hazards mitigable through appropriate strategies, it is imperative to prioritize the development of requisite policies. Furthermore, due emphasis and weight must be accorded to smoking cessation initiatives, alongside concerted efforts to augment the quantity, quality, and accessibility of training programs. Additionally, there is a pressing need for the undertaking of more comprehensive scientific research endeavors aimed at elucidating this multifaceted issue. Such concerted actions are indispensable for the effective mitigation of the adverse impacts of smoking and tobacco addiction on public health.

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REFERENCES

1. Ngaruiya C, Abubakar H, Kiptui D. et al. Tobacco use and its determinants in the 2015 Kenya WHO STEPS survey. BMC Public Health. 2018;18:1223.
2. World Health Organization. WHO report on the global tobacco epidemic, 2008: the MPOWER package: World Health Organization; 2008. <https://www.who.int/publications/i/item/9789241596282> acces date 10.05.2024.
3. Bilir N. Dünyada ve Türkiye’de tütün kullanımı epidemiyolojisi. In: Tütün ve Tütün Kontrolü. 1st edition. Toraks Kitapları, Ankara, 2010;21-35.
4. Küresel Yetişkin Tütün Araştırması, Türkiye, 2016. <https://halksagligi.hacettepe.edu.tr/duyurular/halkayonelik/kyta2016.pdf> access date 10.05.2024.
5. Schwartz JL. Review and evaluation of methods of smoking cessation, 1969-77. Summary of a monograph. Public Health Rep. 1979;94:558-63.
6. Kutlu R, Vatansav C, Demirbaş N, Taşer S. The frequency of tobacco and tobacco product use in medical faculty students. TJFMPC. 2019;13:219-26.
7. Bozkurt N, Bozkurt AI. Assessment of the Fagerstrom Test for Nicotine Dependence (FTND) used in the determination of nicotine dependence and developing a new test for the nicotine dependence. Pamukkale Medical Journal. 2016;9:45-51.
8. Lewis K, Shin D, Davies G. Smoking habits and attitudes toward tobacco bans among United Kingdom hospital staff and students. Int J Tuberc Lung Dis. 2011;15:1122-6.
9. Shahbazi S, Arif AA, Portwood SG, Thompson ME. Risk factors of smoking among health care professionals. J Prim Care Community Health. 2014;5:228-33.
10. Viegas CA, de Andrade AP, Silvestre Rda S. Characteristics of smoking among physicians in the Federal District of Brazil. J Bras Pneumol. 2007;33:76-80.
11. Twardella D, Brenner H. Lack of training as a central barrier to the promotion of smoking cessation: a survey among general practitioners in Germany. Eur J Public Health. 2005;15:140-5.
12. Kaneita Y, Ohida T, Uchida T. Prevalence and correlates of smoking among Japanese physicians: result from the 2008 survey on the smoking activities of Japan Medical Association members. JMAJ. 2013;56:253-66.
13. HuD, YuJ, ChenF. et al. The Chinese physicians' cardiovascular risk evaluation (care) survey: an assessment of physicians' own cardiovascular risks. Heart Asia. 2010;2:89-94.
14. Ravara SB, Calheiros JM, Aguiar P, Barata LT. Smoking behaviour predicts tobacco control attitudes in a high smoking prevalence hospital: A cross-sectional study in a Portuguese teaching hospital prior to the national smoking ban. BMC Public Health. 2011;11:720.
15. Abbritti G, Folletti I, Gambelunghe A. et al. Reduction of tobacco smoking among physicians of a hospital in central Italy. G Ital Med Lav Ergon. 2012;34:453-5.
16. Underner M, Laforgue A-V, Chabaud F, Meurice J-C. Influence of doctors' smoking habits on minimal advice for smoking cessation. A survey of 369 general practitioners in the department of Vienne, France. Presse Med. 2004;33:927-9.
17. Zafar M. Prevalence of smoking and associated risk factors among medical professionals in hospitals of Karachi, Pakistan. Int J Prev Med. 2014;5:457-62.
18. Demir C, Şimşek Z. Physicians' smoking cessation behavior and related factors. TAF Preventive Medicine Bulletin. 2013;12:501-10.
19. Arpacıoğlu S, Ünübol B. Investigation of changes in alcohol-smoking usage and related situations in the coronavirus outbreak. Cyprus Turkish Journal of Psychiatry & Psychology. 2020;2:128-38.
20. Kayhan Tetik B, Gedik Tekinemre I, Taş S. The effect of the COVID-19 pandemic on smoking cessation success. J Community Health. 2021;46:471-5.
21. Ozgunay SE, Akca F, Karasu D. et al. Evaluation of fear levels of anesthetists and prophylaxis practices in the coronavirus (COVID-19) pandemic. JARSS. 2021;29:25-31.
22. Serez B. Smoking prevalence and related factors in Trakya University health personel. Dissertation, Trakya University, Edirne, 2013.
23. Koç EM, Başer D, Döner P. et al. Determining smoking level of hospital employees and the evaluation of the smoke-free air zone applications. JCEI. 2015;6:33-9.
24. Baltacı D, Bahcebasi T, Aydın LY. et al. Evaluation of smoking habits among Turkish family physicians. Toxicol Ind Health. 2014;30:3-11.
25. Aliskin O, Savas N, Inandi T. et al. Smoking status and level of addiction of health workers in Mustafa Kemal University Hospital. Mustafa Kemal Üniv Tıp Derg. 2015;6:32-42.
26. Cerci CT. Smoking status of family physicians and their knowledge, attitudes and behaviours about smoking cessation treatment. Dissertation. Başkent University, Ankara, 2017.
27. Keten HS, Kahraman H, Üçer H. et al. Knowledge, attitudes and practices of family physicians about smoking cessation. Türk Aile Hek Derg. 2014;18:58-62.
28. Eroğlu SA. Health professionals' smoking status and influencing factors in a general state hospital in Istanbul. İst Med J. 2013;14:170-4.
29. Mutlu P, Çeldir Emre J, Dirican N. et al. Hastane personelinde meslek gruplarına göre sigara içme durumu ve sigara bırakma danışma hizmetleri ile ilgili bilgi düzeyleri. Troia Tıp Dergisi. 2019;1:13-9.
30. Global Adult Tobacco Survey 2016. <https://extranet.who.int/ncdsmicrodata/index.php/catalog/872> access date 10.05.2024.

31. Ozyurt L. Some aspects of physicians' smoking behaviour evaluation in terms of variables, Gazi University Medical Faculty Example. Master's thesis, Gazi University, Ankara, 2006.
32. Salepçi B, Fidan A, Çağlayan B. et al. Smoking rates of health care workers at a general training hospital in İstanbul and their attitudes and knowledge about smoking. Solunum. 2006;8:156-62.



Depression Conditions of the Elderly Living in Nursing Homes and the Factors Affecting Them

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Abstract

Aim: The aim of our article is to determine the depression status of elderly people living in nursing homes and the affecting factors.

Material and Method: The study included 75 elderly individuals who lived in assisted living facilities. Data was collected through a Personal Information Form, the Geriatric Depression Scale, the Mini Mental Assessment Test, and retrospective blood results. The data were analyzed using SPSS 26.0 software and non-parametric tests were used due to the non-normal distribution of the data. The Mann-Whitney U test and the Kruskal-Wallis test were used to compare independent variables. Additionally, multiple regression analysis was employed.

Results: The study found that 38.7% of elderly participants had abnormal mini-mental assessments, and 21.3% had significant depression. Statistical analysis revealed significant differences in the total mean scores of the Mini Mental State Test (MMST) based on gender ($p=0.023$), marital status ($p=0.001$), educational attainment ($p=0.001$), and level of schooling. Additionally, there was a statistically significant difference ($p=0.002$) between the Geriatric Depression Scale (GDS) total mean score and the presence of sleep issues. The total mean scores of MMST indicated a statistically significant difference between the status of urine incontinence ($p=0.001$) and exercise ($p=0.006$), as well as their combination.

Conclusion: Approximately one third of the participants were depressed and had poor cognitive status. Depression was associated with being female, low educational status and sleep problems, whereas mental status was associated with gender, marital status, and educational status. It is recommended to conduct longitudinal studies with larger samples in future studies.

Keywords: Depression, nursing home, mental status, elderly

INTRODUCTION

Population ageing is a global issue of our time. Due to technological advancements, declining birth rates, and improved diagnostic and treatment options, people are living longer, resulting in a larger aging population. The world's aging rate has significantly increased in recent years (1). In the final stages of life, some elderly individuals may choose to reside in a nursing home, which can increase the risk of depression. Depression is a prevalent psychological issue among nursing home residents. Research indicates that older adults are at a higher risk of depression than younger adults due to factors such as social isolation, physical health problems, and life changes (2). The estimated prevalence of depression in elderly

individuals in our society is 35% (3). Depression has been linked to accelerated cognitive impairment and disability (4). Social and emotional isolation, chronic diseases, physical health problems, and life changes, such as a change in lifestyle and adaptation to a new environment, may affect the development of depression among elderly people living in nursing homes (5). The diagnosis and treatment of depression can be guided by depression scales, which are part of a detailed geriatric assessment (6). To cope with depression, it is important to strengthen social connections, increase physical activity, and receive psychosocial and emotional support (2,5,7).

Nutritional status of elderly individuals affects both their physical functions and mental health (8). In

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addition, deficiencies in physical functions and cognitive dysfunction also lead to nutritional disorders. In a study conducted on the elderly, it was reported that there was a positive correlation between nutritional status and mental status (9). Psychological, medical, and socioeconomic problems experienced in old ages affect the occurrence of malnutrition. Failure to recognize malnutrition early and not intervening them lead to increases in mortality and morbidity in old ages (10). It seems that depression and nutritional disorders are conditions that can trigger each other. In this sense, it is thought that our study would contribute to the literature.

This article aims to determine the cognitive and mental states of elderly individuals residing in nursing homes, as well as the factors that influence them.

According to this objective, the study aims to provide answers to the following questions:

1. What are the depression levels of elderly people staying at a nursing home?
2. What are the factors affecting the depression levels of the elderly living in a nursing home?

MATERIAL AND METHOD

Study Design

This descriptive study included 97 elderly residents from a nursing facility located in the city center. As a result of the power analysis, the sample size is 73 with a 5% margin of error and a 90% confidence interval. 75 elderly participants participated in the study.

Data Collection

The study was conducted between November and January 2023 with 75 elderly participants. The questionnaire took approximately 7-10 minutes to complete and it was administered face-to-face by the researchers. Blood values were obtained retrospectively from the health records, with the last measurements serving as the basis. No invasive interventions were performed on the elderly.

Inclusion criteria;

- Being over 65 years of age,
- Residing for a minimum of a year in a nursing home,
- Passing the mental test conducted by the nursing home

Exclusion criteria;

- Having reading and comprehension problems

Measurements

Data were gathered using the Personal Information Form, Geriatric Depression Scale Questionnaire, and Mini Mental Assessment Test.

Personal Information Form: The researchers prepared the personal information form in accordance with the literature. The form comprises nine questions that assess

the sociodemographic and other characteristics of elderly individuals participating in the study.

Geriatric Depression Scale (GDS): Burke et al. (1991) tested the validity and reliability of the 15-question short form of the scale developed by Yesavage et al. (1983) from its original 30 items. In the Turkish validity and reliability study, Ertan et al. (1997) reported a Cronbach alpha coefficient of 0.90 for the scale. The questions inquiring about the mood of elderly individuals are answered based on their feelings in the last week. The depression score is determined by answering the questions with either 'yes' or 'no', similar to the long form. Each 'yes' answer is worth one point, and the total score is used to determine the severity of depressive symptoms. Durmaz et al. (2018) suggested that the scoring should be categorized as follows: no depressive symptoms (0-4), mild depressive symptoms (12,13), moderate depressive symptoms (9-11), and severe depressive symptoms (12 or higher) (10). The present study reported a Cronbach alpha coefficient of 0.83 for the scale.

Mini Mental State Test (MMST): The Standardized Mini-Mental Test is used to evaluate cognitive disorders in both educated and uneducated individuals (14). The test consists of six sections: orientation, recording, attention-calculation, recall, language, and structuring, with each question worth one point and a total possible score of 30. The cut-off score for the test is 23. Ertan et al. (1999) modified and created this test (15).

Data Analysis

The statistical analyses were conducted using the SPSS 26.0 software package for Windows. The data's normal distribution was evaluated using the Skewness and Kurtosis (± 1) distribution test (16). To compare independent variables and evaluate the data obtained in the study, Kruskal-Wallis and Mann-Whitney U tests were used due to the non-normal distribution of the data. Additionally, multiple regression analysis was conducted to determine the effects between the variables. The internal consistency Cronbach alpha coefficient was also calculated.

Ethics Committee Approval

Ethics committee approval for this study was received from Gaziantep İslam Science and Technology University (Date: 20 July 2023, Number: 2023/273.27.04).

RESULTS

It was found that 36 percent of the elderly were at least 80 years old, 66.7% were male, 89.3% had no partner, and 78.7% had primary school education. It was found that 40% of the elderly had urinary incontinence, 16% had fecal incontinence, 42.7% had sleeping problems, 29.3% used sleeping pills, and 69.4% did not exercise. It was determined that 21.3% of the elderly were moderately depressed and 38.7% had abnormal mini mental assessment (Table 1).

The total mean score of GDS did not change statistically significantly ($p < 0.05$) based on the elderly's ages and marital statuses. Statistically significant differences were found between the GDS total mean score, gender ($p = 0.012$), and educational level ($p = 0.016$). Furthermore, there was no statistically significant difference ($p < 0.05$) between the ages of the elderly and their MMST total mean score. The results of the statistical analysis showed that the MMST total mean scores varied significantly according to the factors of gender ($p = 0.023$), marital status ($p = 0.001$), and educational level ($p = 0.001$) (Table 2).

Between the total mean score of GDS and the following variables: exercise, use of sleeping pills, fecal incontinence, and urinary incontinence ($p < 0.05$), there were no statistically significant differences. The GDS total mean scores showed statistically significant differences according to the status of experiencing sleeping problems

($p = 0.002$). Fecal incontinence, sleeping problems, and use of sleeping pills did not significantly differ from the MMST total mean score ($p < 0.05$). The MMST total mean scores showed a statistically significant difference between the urinary incontinence ($p = 0.001$), exercise status ($p = 0.006$), and both. Subsequent investigation revealed a significant difference ($p = 0.001$) between the groups who exercised frequently and those who did not (Table 3).

The GDS levels of the elderly ($F = 2.916$; $p = 0.006$) explained 35.1% of the effect on sociodemographic and some other characteristics. In addition, MMST levels ($F = 5.456$; $p = 0.001$) explained 34.3% of the effect on sociodemographic and some other characteristics. When the beta coefficients were analysed, it was seen that sleeping problems explained the level of GDS and the urinary and fecal incontinence explained the level of MMST (Table 4).

Table 1. Distribution of sociodemographic and other characteristics of the elderly and their GDS and MMST (n=75)

Characteristics	n	%	
Age	60-69 years	22	29.3
	70-79 age range	26	34.7
	Age 80 and over	27	36.0
Gender	Female	25	33.3
	Male	50	66.7
Marital status	Has got a partner	8	10.7
	Hasn't got a partner	67	89.3
Level of education literate	Literate	16	21.3
	Primary School	59	78.7
Urinary incontinence	Present	30	40.0
	Absent	45	60.0
Fecal incontinence	Present	12	16.0
	Absent	63	84.0
Sleeping problems	Present	32	42.7
	Absent	43	57.3
Use of sleeping pills	Present	22	29.3
	Absent	53	70.7
Exercise status	Exercises regularly	13	17.3
	Doesn't exercise	52	69.4
	Exercises occasionally	10	13.3
GDS	Normal	37	49.3
	Low	15	20.0
	Moderate	16	21.3
	Severe	7	9.4
MMST	Abnormal	29	38.7
	Normal	46	61.3

Table 2. The comparisons of sociodemographic characteristics of the elderly and total mean scores of GDS and MMST			
		GDS	MMST
		X±SD	X±SD
Age	60-69 years	4.55±4.77	23.77±5.10
	70-79 years	4.54±4.47	23.85±5.65
	80 and over	6.41±4.88	20.30±7.54
Significance		*KW=2.548 p=0.28	KW=4.152 p=0.125
Gender	Female	7.16±4.81	18.84±5.83
	Male	4.24±4.43	24.40±5.90
Significance		**Z=-2.512 p=0.012	Z=-2.127 p=0.023
Marital status	Has got a partner	7.38±4.59	23.63±6.18
	Hasn't got a partner	4.96±4.72	22.42±6.46
Significance		Z=-1.550 p=0.121	Z=3.777 p=0.001
Educational level	Literate	7.63±4.50	16.69±5.85
	Primary School	4.56±4.62	24.14±5.61
Significance		Z=-2.402 p=0.016	Z=-4.055 p=0.001

*KW=Kruskal Wallis Test, **Z=Mann-Whitney U Test, p<0.05. GDS: Geriatric Depression Scale, MMST: Mini Mental State Test.

Table 3. The comparisons of incontinence, sleep, and exercise statuses of the elderly with the total mean scores of GDS and MMST			
		GDS	MMST
		X±SD	X±SD
Urinary incontinence	Present	6.47±4.74	19.10±6.93
	Absent	4.38±4.59	24.84±4.89
Significance		*Z=-1.920 p=0.055	Z=-3.662 p=0.001
Fecal incontinence	Present	6.58±4.40	22.58±7.44
	Absent	4.95±4.78	22.54±6.26
Significance		Z=-0.995 p=0.320	Z=-0.145 p=0.885
Sleeping problems	Present	7.16±4.25	21.03±6.71
	Absent	3.77±4.60	23.67±6.00
Significance		Z=-3.148 p=0.002	Z=-1.714 p=0.086
Use of sleeping pills	Present	5.91±4.66	20.59±6.40
	Absent	4.92±4.72	23.36±6.29
Significance		Z=-1.009 p=0.313	Z=-1.874 p=0.061
Exercise status	Exercises regularly	3.77±3.96	26.23±1.73 (A)
	Doesn't exercise	6.06±4.87	20.98±6.74 (B)
	Exercises occasionally	2.70±3.83	25.90±5.48
Significance		**KW=5.807 p=0.055	KW=10.093 p=0.006

*Z=Mann-Whitney U Test, **KW=Kruskal Wallis Test, p<0.05. GDS: Geriatric Depression Scale, MMST: Mini Mental State Test.

Table 4. The effects of GDS and MMST total scores on sociodemographic and some other characteristics according to multiple regression analysis

	GDS		MMST	
	B	p	B	P
Invariant	16.695	0.018	0.043	0.619
Age	-0.50	0.482	0.039	0.645
Gender	-1.474	0.259	2.126	0.179
Marital status	-3.331	0.068	-0.021	0.992
Educational level	-2.410	0.088	4.643	0.008
Urinary incontinence	0.327	0.804	-5.710	0.001
Fecal incontinence	1.842	0.271	4.217	0.039
Sleeping problems	3.085	0.005	-0.443	0.733
Use of sleeping pills	0.283	0.804	1.492	0.282
Exercise status	-1.099	0.245	0.661	0.562
	R=0.536		R=0.656	
	R2=0.287		R2=0.430	
	Adjusted R2=0.351		Adjusted R2=0.343	
	F=2.916		F=5.456	
	p=0.006		p=0.001	

*Regression test. GDS: Geriatric Depression Scale, MMST: Mini Mental State Examination Test.

DISCUSSION

In this study, the depression levels of elderly patients in Gaziantep Nursing Home Elderly Care and Rehabilitation Center were evaluated and the variables that may affect these conditions were examined. According to the findings, 9.4% of the elderly had severe depression and 21.3% had moderate depression. According to Zhao et al., 26% of elderly citizens living in nursing homes reported having depression-related symptoms (2). When Seddign et al. looked at the depression status of elderly people who were attending daycare centers, living in nursing homes, and staying at their homes, they discovered that those who were in nursing homes had the greatest degree of depression (17). According to research that is comparable to ours, older people who reside in nursing homes have higher rates of depression than those who live at their own homes (18,19). It is believed that residing in a nursing home has a negative impact on an individual's psychological well-being due to the burden of living away from the family and in an institutional setting.

The study revealed that 38.7% of elderly individuals residing in the nursing home had an abnormal mini-mental assessment. Research conducted in our country indicates that the cognitive and mental statuses of elderly individuals living in nursing homes are worse than those living in their own homes (20,21). Additionally, studies conducted in various countries suggested that the cognitive statuses of elderly individuals living in daycare centers or their own homes are better than those living in nursing homes (19,22). These findings align with previous research indicating that institutionalization-based factors contribute to depression,

functional dependence, and cognitive impairment in elderly individuals residing in nursing homes. Additionally, social isolation resulting from the lack of participation in recreational and social activities, infrequent visits from family and friends, and inadequate social support are believed to have negative mental and psychological effects on older adults.

Our study found that age and marital status did not have an effect on the depression levels of elderly individuals living in the nursing home. This is supported by the results of Pokharel et al. (23). However, it is generally believed that depression in the elderly is influenced by age and marital status (24,25). Research suggests that single individuals between the ages of 70-74 are more likely to experience depression while residing in nursing homes (23-27). In Türkiye, cultural norms and circumstances may lead elderly individuals, who have lost their spouses, to choose or be required to reside in nursing homes, despite not being a common situation. The analyzed population is believed to be predominantly single, and their lack of social support increases the risk of depression across all age groups. Korkmaz and Ümmet (28) suggested that residing in a nursing home may lead to the feelings of abandonment and loneliness among the elderly. Therefore, when interpreting the relationship between depression and age in elderly groups, it is important to consider the loneliness and social support perceptions of elderly individuals.

The study indicated that depression is influenced by gender and educational level. Women and individuals with lower educational levels tend to have higher depression scores. This finding is consistent with previous studies

that have found higher rates of depression among women in nursing homes compared to men (29,30). Research has shown that women are more susceptible to depression than men (31). Additionally, studies have found that women generally prefer to live at their own homes with their families and have negative attitudes towards nursing homes (32). Furthermore, individuals with higher levels of education tend to have more positive attitudes towards the physical, social, and psychological changes that come with aging, resulting in fewer psychosocial effects (33). This result suggests that educational level may be related to adaptation to age-related changes and maintaining positive attitudes towards aging. However, it is important to note that education is not the sole factor influencing this situation.

The study found that age did not have a significant effect on the mental state of elderly individuals. However, gender, marital status, and educational level were found to be influential factors. Previous studies have also highlighted that women, widows, divorced, or single individuals tend to have worse mental health (34). Additionally, there is a significant correlation between cognitive impairment and depressive symptoms. Depression was observed at a higher rate in women and single women in the study. It may have affected cognitive decline and led to the emergence of physical, psychological, and social symptoms. One possible risk factor for the beginning of dementia and cognitive impairment is depression symptoms.

It was observed that urinary incontinence, fecal incontinence, use of sleeping pills, and exercise do not have an effect on depression, but those with sleeping problems were more depressed. It is known that insomnia is seen due to increasing comorbidities in old age. Depression and sleep quality have a two-way relationship. Depression in older adults may begin as a result of poor sleep quality, whereas symptoms of depressive disorders are linked to a higher risk of sleep disorders (insomnia/excessive sleep) (35). Urinary incontinence (UI) and geriatric mental status were found to be correlated linearly, and elderly individuals with UI also tended to have poor mental health. Similar to our research, the prevalence study by Kessler et al. discovered that older individuals with urinary incontinence had low mental and cognitive states (36). Additionally, incontinence was shown to be substantially correlated with cognitive deterioration, elevated anxiety, and depression in other research that examined the association between UI and psycho-cognitive health (37). This suggests that urinary incontinence has a negative effect in many mental and psychosocial areas, although it is not directly related with lifestyle.

It was observed that the mental status of those who exercised regularly was considerably better than those who did not exercise at all. This is similar to the findings of many studies showing that exercise is effective on cognitive and mental health in elderly individuals (38). Previous research demonstrated that exercise may help patients feel better about themselves, prevent cognitive decline, enhance life satisfaction, and lessen symptoms of

anxiety and depression (39). It is thought that exercise may help to improve mental health by reducing stress hormones (40), and helping individuals to establish interpersonal relationships and receive social support.

Limitations

The study population was derived from a single center. Including multiple centers would enhance the overall distribution.

CONCLUSION

It was found that most of the elderly had urinary incontinence and fecal incontinence, had sleeping problems, used sleeping pills, and did not exercise. Approximately one third were depressed and had poor cognitive statuses. Depression was found to be affected by being female, having lower educational level, and sleeping problems, and the mental status was found to be affected by gender, marital status, educational level, having incontinence, and exercise.

In accordance with these findings, it is recommended that a needs analysis and problem screening studies should be conducted to accurately identify the issues faced by elderly individuals with high levels of mental decline and depression in nursing homes. It is also suggested that such studies should be conducted with large sample sizes to ensure accuracy. Solution proposals should be developed for the emerging problems and needs. In addition, psycho-education programmes should be developed and implemented for the elderly with depression. Finally, there is a need for research aiming to explore the different dimensions of the mental and depression states of the elderly.

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Ethical approval: Ethics committee approval for this study was received from Gaziantep İslam Science and Technology University (Date: 20 July 2023, Number: 2023/273.27.04). In addition, institutional permission was obtained from the relevant institutions to conduct the research. The elderly individuals were informed before the study and their written consent was obtained, and participation in the study was based on voluntariness. This study was conducted in accordance with the Principles of the Declaration of Helsinki.

REFERENCES

1. BM: Leaving No One Behind In An Ageing World. <https://social.desa.un.org/publications/2023-leaving-no-one-behind-in-an-ageing-world> access date 10.02.2024.
2. Zhao X, Zhang D, Wu M, et al. Loneliness and depression symptoms among the elderly in nursing homes: a moderated mediation model of resilience and social support. *Psychiatry Res.* 2018;268:143-51.

3. Bulut EA, Soysal P, Isik AT. Frequency and coincidence of geriatric syndromes according to age groups: single-center experience in Turkey between 2013 and 2017. *Clin Interv Aging*. 2018;13:1899-905.
4. Potter GG, McQuoid DR, Whitson HE, Steffens DC. Physical frailty in late-life depression is associated with deficits in speed-dependent executive functions. *Int J Geriatr Psychiatry*. 2016;31:466-74.
5. Jahouh M, González-Bernal JJ, González-Santos J, et al. Impact of an Intervention with Wii video games on the autonomy of activities of daily living and psychological-cognitive components in the institutionalized elderly. *Int J Environ Res Public Health*. 2021;18:1570.
6. Mutlay F, Ulusoylar Erken N, Dost Günay FS, et al. May depression be associated with the frequency of falls in the elderly?. *Journal of Geriatric Science*. 2020;3:103-9.
7. Pearce M, Garcia L, Abbas A, et al. Association between physical activity and risk of depression: a systematic review and meta-analysis. *JAMA Psychiatry*. 2022;79:550-9.
8. Balcı E, Şenol V, Eşel E. et al. The relationship between malnutrition and depression in people aged over 65 years. *Turkish Journal of Public Health*. 2012;10:37-43.
9. Slavíková M, Procházka B, Dlouhý P, et al. Prevalence of malnutrition risk among institutionalized elderly from North Bohemia is higher than among those in the Capital City of Prague, Czech Republic. *Cent Eur J Public Health*. 2018;26:111-7.
10. Özer E, Kapucu S. Malnutrition and related risk factors of elderly people. *Akad Geriatri*. 2013;5:5-11.
11. Burke WJ, Roccaforte WH, Wengel SP. The short form of the Geriatric Depression Scale: a comparison with the 30-item form. *J Geriatr Psychiatry Neurol*. 1991;4:173-8.
12. Ertan T, Eker E, Şar V. Validity and reliability of the geriatric depression scale in the Turkish elderly population. *Archives of Neuropsychiatry*. 1997;34:62-71.
13. Durmaz B, Soysal P, Ellidokuz H, Isik AT. Validity and reliability of geriatric depression scale-15 (short form) in Turkish older adults. *North Clin Istanbul*. 2018;5:216-20.
14. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state" A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-98.
15. Ertan T, Eker E, Güngen C, et al. The standardized mini mental state examination for illiterate Turkish elderly population. 2nd International Symposium on Neurophysiological and Neuropsychological Assessment of Mental and Behavioral Disorders; 1999. Bursa, Türkiye.
16. George D. SPSS for windows step by step: a simple study guide and reference, 17.0 update, 10/e. Pearson Education India, 2011.
17. Seddigh M, Hazrati M, Jokar M, et al. A comparative study of perceived social support and depression among elderly members of senior day centers, elderly residents in nursing homes, and elderly living at home. *Iran J Nurs Midwifery Res*. 2020;25:160-5.
18. Fonseca C, de Pinho LG, Lopes MJ, et al. The elderly nursing core set and the cognition of portuguese older adults: a cross-sectional study. *BMC Nurs*. 2021;20:108.
19. Mannucci PM, Nobili A, Investigators R. Multimorbidity and polypharmacy in the elderly: lessons from REPOSI. *Intern Emerg Med*. 2014;9:723-34.
20. Dağhan Ş, Arabacı Z, Hasgül E. Investigation of home accidents in elderly according to cognitive situation and related factors. *Journal of Social Policy Studies*. 2017;17:75-95.
21. Tarsuslu Şimşek T, Tütün Yümin E, Sertel M, et al. Effects of mental, functional and mobility disabilities on the health related quality of life and life satisfaction in elderly individuals: a comparative study. *Turkish Journal of Geriatrics*. 2011;14:321-30.
22. Del Duca GF, Silva SGd, Thumé E, et al. Predictive factors for institutionalization of the elderly: a case-control study. *Rev. saúde pública*. 2012;46:147-53.
23. Pokharel B, Sharma B. Depression and its associated risk factors among residents of a geriatric home in Western Nepal. *J Lumbini Med Coll*. 2019;7:24-8.
24. Šare S, Ljubičić M, Gusar I, et al. Self-esteem, anxiety, and depression in older people in nursing homes. *Healthcare*. 2021;9:1035.
25. Polat F, Karasu F. The Relationship between Perceived Loneliness Level and Depression Among Elderly Individuals. *Journal of Inonu University Health Services Vocational School*. 2020;8:72-82.
26. Manungkalit M, Sari NPWP. The influence of anxiety and stress toward depression in institutionalized elderly. *Journal of Educational Health and Community Psychology*. 2020;9:65-76.
27. Chalise HN. Depression among elderly living in Briddashram (old age home). *Advances in Aging Research*. 2014;3:6-11.
28. Korkmaz T, Ümmet D. Investigation of the relationship between perception of loneliness and quality of life of the elderly in nursing home. *MANAS Journal of Social Studies*. 2021;10:463-75.
29. Sapkota N, Khadka B, Tiwari A, Poudel A. Prevalence of Depression among Residents of old age homes in Eastern Nepal. *J Psychiatrists' Association of Nepal*. 2019;8:39-44.
30. Zalavadiya DD, Banerjee A, Sheth AM, et al. A comparative study of depression and associated risk factors among elderly inmates of old age homes and community of Rajkot: a Gujarati version of the geriatric depression scale-short form (GDS-G). *Indian J Community Med*. 2017;42:204-8.
31. Salk RH, Hyde JS, Abramson LY. Gender differences in depression in representative national samples: meta-analyses of diagnoses and symptoms. *Psychol Bull*. 2017;143:783-822.
32. Şenol D, Erdem S. The old age and the perception of nursing home in elderly women: a qualitative study. *Kırıkkale University Journal of Social Sciences*. 2017;7:31-50.
33. Marquet M, Missotten P, Schroyen S, et al. A validation of the French version of the Attitudes to Aging Questionnaire (AAQ): factor structure, reliability and validity. *Psychol Belg*. 2016;56:80-100.
34. Cordeiro RC, Santos RCd, Araújo GKNd, et al. Mental health profile of the elderly community: a cross-sectional study. *Rev Bras Enferm*. 2020;73:e20180191.

35. Palteki AS, Aykaç E, Yükselen N, et al. Sleep quality and depression of older people living at care home. ESTÜDAM Journal of Public Health. 2021;6:105-13.
36. Kessler M, Facchini LA, Soares MU, et al. Prevalence of urinary incontinence among the elderly and relationship with physical and mental health indicators. Revista Brasileira de Geriatria e Gerontologia. 2018;21:397-407.
37. Cheng S, Lin D, Hu T, et al. Association of urinary incontinence and depression or anxiety: a meta-analysis. J Int Med Res. 2020;48:300060520931348.
38. Schrader B, Bünker A-M, Conradi C, et al. Regular exercise is associated with a more favorable cardiovascular risk profile, better quality of life, less depression and less psychological stress. Int J Gen Med. 2022;15:545-54.
39. Kramer A. An overview of the beneficial effects of exercise on health and performance. Adv Exp Med Biol. 2020;1228:3-22.
40. Diamond R, Waite F. Physical activity in a pandemic: a new treatment target for psychological therapy. Psychol Psychother. 2021;94:357-64.



Investigation of the Relationship Between Exercise Barriers, Quality of Life, Physical Performance, and Range of Motion in Patients with Total Hip Arthroplasty

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Abstract

Aim: This study aimed to demonstrate the relationship between exercise barriers-benefits with joint range of motion (ROM), quality of life, and physical performance in individuals with total hip arthroplasty (THA).

Material and Method: A cross-sectional observational study was conducted with fifty older individuals with THA. Patients were evaluated with the 5-Times Sit and Stand Test (5TSTS), Exercise Benefits and Barriers Scale (EBBS), and EuroQol (EQ-5D-5L) Quality of Life Scale. In addition, the patient's active ROM was measured with a universal goniometer.

Results: There was a significant low correlation between body mass index (BMI) and EBBS-Benefits sub-score ($r=-0.286$, $p<0.05$). EQ-5D-5L VAS was weakly correlated with EBBS ($r=-0.291$, $p<0.05$). 5TSTS was moderately correlated with EBBS Barriers sub-score, EBBS Benefits sub-score, and EBBS total score, respectively ($r_1=0.354$, $r_2=0.440$, $r_3=0.444$, $p_1<0.05$, $p_{2,3}<0.01$). EBBS Barriers sub-score strongly correlated with EBBS Benefits sub-score and EBBS total score, respectively ($r_1=0.709$, $r_2=0.826$, $p<0.01$). In addition, the EBBS Benefits sub-score was highly correlated with the EBBS total score ($r=0.983$, $p<0.01$). There was a low to moderate correlation between the EBBS Barriers sub-score and all active ROM measures ($p<0.05$).

Conclusion: Individuals' exercise barriers and benefits were mainly associated with physical performance. Participants with higher exercise benefits from exercise had higher physical performance, ROM, and quality of life.

Keywords: Function, exercise barriers, exercise benefits, joint motion, life quality

INTRODUCTION

Total hip arthroplasty (THA) is a frequent surgical procedure preferred to reduce pain and improve the function of patients with hip osteoarthritis (1,2). The survival rate in the postoperative period is between 98% and 100% due to recent surgical techniques, including cementless prosthesis design and cross-linked polyethylene (3,4). However, despite these advances in surgical practice, patients may experience decreased muscle strength and quality of life (5,6). Recent studies indicate that these deficiencies occur in 10-20% of individuals with THA (7). Therefore, patients should be assessed holistically during the rehabilitation process.

Objective and subjective measurements are used in evaluating individuals with THA. Performance-based

clinical tests are commonly used to evaluate patients objectively. These tests demonstrate the individual's functional independence (8). A study has reported that the improvements shown by performance-based clinical tests used in evaluating individuals with THA do not coincide with the results of patient-reported outcomes measures (PROMs) (9). However, it has also been remarked that a causal relationship exists between performance-based and PROMs (10).

Some assessments can only be fulfilled through the subjective interpretation of individuals. One of these is patients' exercise perception. Exercise programs given to individuals with THA in the postoperative period are more effective than other rehabilitation approaches in reducing pain and improving muscle strength, function, and other clinical outcomes (11). A recent study reported

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that identifying the benefits and barriers affecting the individual's exercise habit and adaptation to training can enable rehabilitation professionals, especially physiotherapists, to provide practical rehabilitation approaches. In addition, these assessments may enable individuals to develop clinical exercise practice recommendations to accelerate the recovery of individuals and increase their quality of life (12,13).

The literature does not provide adequate evidence to provide exercise facilitators and barriers in individuals with THA (12). In addition, objective and subjective aspects of the measurements are not compared regarding causal relationships in individuals with THA. Exercise barriers, physical performance, and quality of life are not presented with relevant clinical outcomes in individuals with THA. This study aimed to demonstrate the relationship between exercise barriers-benefits with joint range of motion, quality of life, and physical performance in individuals with THA.

MATERIAL AND METHOD

Subjects and Clinical Setting

The cross-sectional observational study was conducted in the Orthopaedics and Traumatology Department of the Muğla Training and Research Hospital between February and June 2022. Fifty patients with THA (71.38±9.91 years, 33 women, and 17 men) participated in the study. The inclusion criteria of the study were; (1) patients at least six months after the THA, (2) patients with primary THA, (3) patients who can understand and respond to verbal commands, (4) patients who do not have hearing, speech, or psychiatric problems that prevent communication. The exclusion criteria of the study were; (1) patients with revision surgery, (2) patients with THA for reasons such as rheumatoid arthritis and traumatic injury, (4) patients with a history of other lower limb surgery or a disease such as stroke that may affect the assessments, (5) patients with post-operative complications such as deep vein thrombosis. The study was carried out in accordance with the ethical principles and the Helsinki Declaration. Informed consent of the patients was obtained. The study protocol was approved by Ege University Medical Research Ethics Committee (No: 22-8.1T/63). G*Power software was used to calculate the effect size. The effect size was based on the medium effect size (0.50) of Cohen's d, with an error probability of 0.05 and a statistical power of 0.95, which were used during the calculation. Finally, a minimum of 34 cases were calculated as required for the research sample (14).

Procedures

Individual characteristics (e.g., age, gender, height, weight, chronic disease status, education level) were recorded. Patients were evaluated with the 5-Times Sit and Stand Test (5TSTS), Exercise Benefits and Barriers Scale (EBBS), and EuroQol (EQ-5D-5L) Quality of Life Scale. In addition, the patient's active range of motion (ROM) was measured with a universal goniometer.

5-Times Sit and Stand Test

Participants stand up and sit down as quickly as possible five times from a 43 cm highchair without armrests. A stopwatch is used to calculate the time (15).

Exercise Benefits and Barriers Scale

The EBBS consists of 43 items. Twenty-nine questions address the benefits of exercise, and 14 questions address the barriers to exercise. The scale was designed according to a 4-point Likert-type scale: "strongly agree (4), agree (3), disagree (2), strongly disagree (1)". The benefit subscale ranges between 29 and 116, and the barrier subscale ranges between 14 and 56. The total score ranges from 43-172. In this scoring system, a higher score represents a higher perception. The Turkish validity and reliability of the scale were conducted by Ortabağ et al. (16).

EQ5D5L Quality of Life Scale

The EQ-5D-5L consists of 2 parts: EQ-5D descriptive system and EQ visual analog scale (EQ VAS). The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels: no problem, mild problem, moderate problem, severe problem, and extreme problem. The patient is asked to indicate their health status by checking the box next to the most appropriate statement in each of the five dimensions. The EQ VAS records the patient's health status on a vertical visual analog scale, where the endpoints are labeled "best health you can imagine" and "worst health you can imagine". The VAS can be used as a quantitative measure of health outcomes reflecting the patient's judgment (17).

Active Range of Motion Measurements

A universal goniometer was used for all ROM measurements at the functional range of motion limit. The measurement directions were internal rotation, external rotation, flexion, extension, and abduction.

Internal/External Rotation

The patients are instructed to turn their legs outward and inward while sitting. The fulcrum was aligned with the patella, and both arms of the goniometer were within the midline of the tibia. The stationary arm was then hanging freely but should be perpendicular to the floor (18).

Flexion/Extension

The participant was asked to lie supine and prone. The measurement was then performed with the fixed arm positioned along the lateral midline of the abdomen, using the pelvis as a reference, and the goniometer's movable arm along the lateral midline of the femur (18).

Abduction

Hip abduction was measured from the neutral zero position, where the longitudinal axis of the thigh was perpendicular to the transverse line along the anterior superior iliac spines of the pelvis. These last anatomical landmarks were also used to align the fixed arm of the goniometer. The movable arm was aligned on the midline

of the femur, pointing to the center of the patella (19).

Statistical Analysis

SPSS for Windows v25.0 software (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. For quantitative variables, mean and standard deviation (SD) were presented. Percent (%) were reported for qualitative variables. The normal distribution of data was analyzed by Shapiro-Wilk or Kolmogorov–Smirnov tests. The skewness and kurtosis coefficients were considered to determine whether the data followed a normal distribution.

The relationship between variables was analyzed using Pearson correlation analysis. The Mann-Whitney U test presented the differences in active range of motion between affected sides. A significance level of $p < 0.05$ was considered statistically significant.

RESULTS

A total of 50 patients with THA (71.38 ± 9.91 years, 33 women, 17 men) participated in the study. Demographic and clinical characteristics of the participants are detailed in Table 1.

Table 1. The baseline physical and clinical characteristics of the participants

	THA patients (n=50)
Age (years, mean \pm SD)	71.38 \pm 9.91
Gender (women/men, n (%))	33 (66)/17 (34)
BMI (kg/m ² , mean \pm SD)	27.43 \pm 4.68
Affected side (right/left, n (%))	24 (48)/26 (52)
Living area (urban/rural, n (%))	31 (62)/19 (38)
Education status (primary/high school and above, n (%))	40 (80)/10 (20)
Smoking (yes/no, n (%))	5 (10)/45 (90)
Duration after THA surgery (months, mean \pm SD)	23.62 \pm 21.76
Presence of chronic disease (present/absent, n (%))	38 (76)/12 (24)

SD: standard deviation, n: number of patients, BMI: body mass index, THA: total hip arthroplasty

Relationship Between Parameters

Pearson correlation analysis was carried out to reveal the relationship between the parameters. Table 2 shows the correlation coefficients between EBBS with 5TSTS, EBBS, and EQ-5D-5L. The correlation between the active ROM measurements and EBBS are summarized in Table 3.

There was a significant low correlation between body mass index (BMI) and EBBS-Benefits sub-score ($r = -0.286$, $p < 0.05$). EQ-5D-5L VAS was weakly correlated with EBBS

($r = -0.291$, $p < 0.05$). 5TSTS was moderately correlated with EBBS Barriers sub-score, EBBS Benefits sub-score, and EBBS total score, respectively ($r_1 = 0.354$, $r_2 = 0.440$, $r_3 = 0.444$, $p_1 < 0.05$, $p_{2,3} < 0.01$). EBBS Barriers sub-score strongly correlated with EBBS Benefits sub-score and EBBS total score, respectively ($r_1 = 0.709$, $r_2 = 0.826$, $p < 0.01$). In addition, the EBBS Benefits sub-score was highly correlated with the EBBS total score ($r = 0.983$, $p < 0.01$) (Table 2). There was a low to moderate correlation between the EBBS Barriers sub-score and all active ROM measures ($p < 0.05$) (Table 3).

Table 2. The relationship between clinical test, scale scores and patients' characteristics in THA patients

n: 50	EBBS-Barriers	EBBS-Benefits	EBBS-Total
Age	0.071	0.253	0.221
BMI	-0.171	-0.286*	-0.272
Duration after THA	0.04	-0.081	-0.054
EQ-5D-5L	-0.175	-0.242	-0.239
EQ-5D-5L VAS	-0.101	-0.291*	-0.259
5TSTS	0.354*	0.440**	0.444**

THA: total hip arthroplasty, n: number of patients, BMI: body mass index, EQ-5D-5L VAS: EQ-5D-5L quality of life scale visual analog scale, 5TSTS: Five Times Sit to Stand Test, EBBS: Exercise Benefits and Barriers Scale, *: $p < 0.05$, **: $p < 0.01$, Pearson Correlation Test was used in all analyses

Table 3. Relationship between active range of motion measurements and other parameters

n: 50	RHIR	RHER	RHF	RHE	RHABD	LHIR	LHER	LHF	LHE	LHABD
EBBS-barriers	-0.415**	-0.367**	-0.233	-0.309*	-0.310*	-0.273	-0.280*	-0.117	-0.265	-0.187
EBBS-benefits	-0.423**	-0.479**	-0.313*	-0.319*	-0.371**	-0.517**	-0.358*	-0.345*	-0.316*	-0.384**
EBBS-total	-0.446**	-0.478**	-0.310*	-0.335*	-0.377**	-0.475**	-0.359*	-0.306*	-0.322*	-0.356*

EBBS: Exercise Benefits and Barriers Scale, RHIR: right hip internal rotation, RHER: right hip external rotation, RHF: right hip flexion, RHE: right hip extension, RHABD: right hip abduction, LHIR: left hip internal rotation, LHER: left hip external rotation, LHF: left hip flexion, LHE: left hip extension, LHABD: left hip abduction, *: $p < 0.05$, **: $p < 0.01$, Pearson Correlation Test was used in all analyses

DISCUSSION

The results revealed that exercise barriers and benefits were moderately associated with physical performance. However, exercise benefits were poorly associated with body mass index and quality of life. Finally, there was a low-to-moderate association between benefits and barriers of exercise barrier with hip ROM in all directions. The outcomes of this study revealed that individuals' exercise barriers and benefits were mainly associated with physical performance. Participants with higher exercise benefits from exercise had higher physical performance, ROM, and quality of life. Future studies may address exercise barriers and benefits in the context of secondary data from a randomized controlled trial of a standardized exercise program in the postoperative period.

The sample of this study consisted of older people, with an average age of approximately 71. The female population was higher than expected. More comprehensive cohorts in recent years have also shown more women with THA (20). On the other hand, the individuals were overweight according to BMI classification. The sample did not consist of obese patients. Therefore, the sample was homogenous in terms of BMI. Since the individuals were at least six months after surgery (with a mean of approximately 23 months), a stable period of THA can be observed regarding their physical condition (21). In this respect, our sample is also homogeneous regarding physical performance.

The results of the correlational analysis revealed that exercise barriers and benefits were primarily related to the 5TSTS, indicating the physical performance of the individuals. Subjective exercise perceptions of the patients are shown to be associated with their physical status. Numerous studies have demonstrated that post-operative exercise protocols in THA improve patients' physical function (22-24). These results indicate that that high exercise barrier achievement, particularly in this population of older individuals, may have negative consequences in some cases due to exercise compliance or non-performance of exercises. For example, inadequate stretching exercises may result in permanent loss of ROM (25), or in some cases, lack of aerobic exercise may have a negative impact on quality of life (26).

Exercise benefits were found to have a low correlation with quality of life. Many physical and psychological parameters can affect the quality of life in individuals with THA independently or holistically (27,28). The quality of life may also be affected by pain, disability, activities of daily living and psychological status. However, although a low correlation levels, our results may prove that individuals with THA who report more exercise benefits have a higher quality of life. The minimal clinically important difference (MCID) values of the EQ-5D may be helpful to show that increasing exercise benefits more clearly (29). However, since our study did not have a longitudinal design, we could not demonstrate the clinical significance of this change.

Another subclinical result we obtained from our study was the negative relationship between BMI and exercise benefits. As expected, we found that individuals with lower BMI benefited more from exercise. BMI is already known to be a negative indicator for surgical success after THA (30,31). It is comprehended that individuals with hip osteoarthritis are in a vicious circle regarding aerobic exercise and osteoarthritis progression. In clinical practice, some physicians claim that aerobic exercise such as walking combined with increased load on the joint due to high weight may increase osteoarthritis. In contrast, clinical guidelines strongly recommend aerobic exercise to prevent hip osteoarthritis (32,33). Our study found that individuals with high BMI benefited less from exercise. Future studies should address the barriers and benefits of exercise after THA in individuals with high BMI more comprehensively.

The correlation between ROM and the benefits of exercise barriers provided critical clinical outcomes for comparing objective-subjective parameters in our study. The total score of exercise barriers and benefits was moderate to strongly correlated with all angles of hip joint motion. The highest correlation was with the degree of external rotation. According to these results, it was revealed that ROM is also related to the subjective exercise intake of individuals. Some studies have demonstrated flexion-extension ROM losses with neglect of post-operative rehabilitation protocols (34,35). The subjective exercise perception of individuals supported our results.

Limitations

The study has some potential methodological limitations. First, the fact that individuals' exercise perceptions were not addressed within the context of a standardized exercise rehabilitation protocol. Secondly, our study was conducted with a prospective cross-sectional design. In a longitudinal design, the change between two different measurements in terms of MCID value could have facilitated the clinical interpretation of the results. Although we provide an evidence-based power analysis with a sample size, a higher sample may improve the evidence level of the statistical analysis.

CONCLUSION

The results revealed that exercise barriers and benefits were moderately associated with physical performance. However, exercise benefits were poorly associated with body mass index and quality of life. Finally, there was a low-to-moderate association between benefits and barriers of exercise barrier with hip ROM in all directions. The outcomes of this study revealed that individuals' exercise barriers and benefits were mainly associated with physical performance. Participants with higher exercise benefits from exercise had higher physical performance, ROM, and quality of life. Future studies may address exercise barriers and benefits in the context of secondary data from a randomized controlled trial of a standardized exercise program in the postoperative period.

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Conflict of interest: The authors have no conflicts of interest to declare.

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REFERENCES

- Bakırhan S, Ünver B, Karatosun V. Does preoperative body weight affect early postoperative functional activities in patients with total hip arthroplasty?. *Jt Dis Relat Surg*. 2017;28:188-94.
- Bennett D, Humphreys L, O'brien S, et al. Gait kinematics of age-stratified hip replacement patients—a large scale, long-term follow-up study. *Gait Posture*. 2008;28:194-200.
- Kim YH, Park JW, Patel C, Kim DY. Polyethylene wear and osteolysis after cementless total hip arthroplasty with alumina-on-highly cross-linked polyethylene bearings in patients younger than thirty years of age. *J Bone Joint Surg Am*. 2013;95:1088-93.
- Hanna S, Somerville L, McCalden R, et al. Highly cross-linked polyethylene decreases the rate of revision of total hip arthroplasty compared with conventional polyethylene at 13 years' follow-up. *Bone Joint J*. 2016;98:28-32.
- Dayton MR, Judd DL, Hogan CA, Stevens-Lapsley JE. Performance-based versus self-reported outcomes using the hip disability and osteoarthritis outcome score after total hip arthroplasty. *Am J Phys Med Rehabil*. 2016;95:132-8.
- Wallis J, Webster K, Levinger P, Taylor N. What proportion of people with hip and knee osteoarthritis meet physical activity guidelines? A systematic review and meta-analysis. *Osteoarthritis Cartilage*. 2013;21:1648-59.
- Rolfson O, Kärrholm J, Dahlberg L, Garellick G. Patient-reported outcomes in the Swedish Hip Arthroplasty Register: results of a nationwide prospective observational study. *J Bone Joint Surg Br*. 2011;93:867-75.
- Özden F, Coşkun G, Bakırhan S. The test-retest reliability and concurrent validity of the five times sit to stand test and step test in older adults with total hip arthroplasty. *Exp Gerontol*. 2020;142:111143.
- Naili JE, Hedström M, Broström EW. Changes of and interrelationships between performance-based function and gait and patient-reported function 1 year after total hip arthroplasty. *J Orthop Traumatol*. 2019;20:14.
- Elibol N, Ünver B, Karatosun V, Gunal I. Relationship between self-reported and performance-based tests in assessment of patients with total hip arthroplasty. *Hip Int*. 2018;28:566-70.
- Wu JQ, Mao LB, Wu J. Efficacy of exercise for improving functional outcomes for patients undergoing total hip arthroplasty: a meta-analysis. *Medicine*. 2019;98:e14591.
- Bakaa N, Chen LH, Carlesso L, et al. Understanding barriers and facilitators of exercise adherence after total-knee arthroplasty. *Disabil Rehabil*. 2022;44:6348-55.
- Petursdottir U, Arnadottir SA, Halldorsdottir S. Facilitators and barriers to exercising among people with osteoarthritis: a phenomenological study. *Phys Ther*. 2010;90:1014-25.
- Faul F, Erdfelder E, Lang AG, Buchner A. G* Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*. 2007;39:175-91.
- Özden F, Tümtürk İ. Performance-based outcome measures in total knee arthroplasty: a systematic review. *Phys Occup Ther Geriatr*. 2022;40:241-60.
- Ortabag T, Ceylan S, Akyuz A, Bebis H. The validity and reliability of the Exercise Benefits / Barriers Scale for Turkish military nursing students. *S Afr J Res Sport Phys Educ Recreat*. 2010;32:55-70.
- van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health*. 2012;15:708-15.
- Yazdifar M, Yazdifar MR, Mahmud J, et al. Evaluating the hip range of motion using the goniometer and video tracking methods. *Procedia Eng*. 2013;68:77-82.
- Nussbaumer S, Leunig M, Glatthorn JF, et al. Validity and test-retest reliability of manual goniometers for measuring passive hip range of motion in femoroacetabular impingement patients. *BMC Musculoskelet Disord*. 2010;11:194.
- Delanois RE, Gwam CU, Mistry JB, et al. Does gender influence how patients rate their patient experience after total hip arthroplasty?. *Hip Int*. 2018;28:40-3.
- Slaven EJ. Prediction of functional outcome at six months following total hip arthroplasty. *Phys Ther*. 2012;92:1386-94.
- Moyer R, Ikert K, Long K, Marsh J. The value of preoperative exercise and education for patients undergoing total hip and knee arthroplasty: a systematic review and meta-analysis. *JBJ Rev*. 2017;5:e2.
- Piva SR, Gil AB, Almeida GJ, et al. A balance exercise program appears to improve function for patients with total knee arthroplasty: a randomized clinical trial. *Phys Ther*. 2010;90:880-94.
- Rooks DS, Huang J, Bierbaum BE, et al. Effect of preoperative exercise on measures of functional status in men and women undergoing total hip and knee arthroplasty. *Arthritis Care Res (Hoboken)*. 2006;55:700-8.
- Coudeyre E, Jardin C, Givron P, et al. Could preoperative rehabilitation modify postoperative outcomes after total hip and knee arthroplasty? Elaboration of French clinical practice guidelines. *Ann Readapt Med Phys*. 2007;50:189-97.
- Moffet H, Collet JP, Shapiro SH, et al. Effectiveness of intensive rehabilitation on functional ability and quality of life after first total knee arthroplasty: a single-blind randomized controlled trial. *Arch Phys Med Rehabil*. 2004;85:546-56.
- Ethgen O, Bruyère O, Richey F, et al. Health-related quality of life in total hip and total knee arthroplasty: a qualitative and systematic review of the literature. *J Bone Joint Surg Am*. 2004;86:963-74.

28. Quintana JM, Escobar A, Aguirre U, et al. Predictors of health-related quality-of-life change after total hip arthroplasty. *Clin Orthop Relat Res.* 2009;467:2886-94.
29. Coretti S, Ruggeri M, McNamee P. The minimum clinically important difference for EQ-5D index: a critical review. *Expert Rev Pharmacoecon Outcomes Res.* 2014;14:221-33.
30. Baker P, Petheram T, Jameson S, et al. The association between body mass index and the outcomes of total knee arthroplasty. *J Bone Joint Surg Am.* 2012;94:1501-8.
31. Si H-b, Zeng Y, Shen B, et al. The influence of body mass index on the outcomes of primary total knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc.* 2015;23:1824-32.
32. Williams PT. Effects of running and walking on osteoarthritis and hip replacement risk. *Med Sci Sports Exerc.* 2013;45:1292-7.
33. Bieler T, Siersma V, Magnusson S, et al. In hip osteoarthritis, Nordic Walking is superior to strength training and home-based exercise for improving function. *Scand J Med Sci Sports.* 2017;27:873-86.
34. Murphy MT, Skinner TL, Cresswell AG, et al. The effect of knee flexion contracture following total knee arthroplasty on the energy cost of walking. *J Arthroplasty.* 2014;29:85-9.
35. Tsukagoshi R, Tateuchi H, Fukumoto Y, et al. Factors associated with restricted hip extension during gait in women after total hip arthroplasty. *Hip Int.* 2015;25:543-8.



DTI Measurements for Huntington Disease Using Mricloud

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Abstract

Aim: Neurodegenerative diseases are important health problems that affect many people. In this study, it was aimed to examine the brain regions of Huntington's patients by performing brain parcellation.

Material and Method: 8 controls and 8 Huntington's patients participated in the study. We measured four Diffusion Tensor Imaging metrics which were axial diffusivity, mean diffusivity, radial diffusivity and fractional anisotropy performing brain parcellation over Diffusion Tensor Imaging for control and patient groups. We used a full automated data-driven approach to study the whole brain, divided in regions of interest using mricloud.

Results: When the huntington disease group compared to control group, We found that mean diffusivity and axial diffusivity increased frontal, parietal, temporal, occipital, corpus callosum, white matter, limbic and subcortical structures, and radial diffusivity increased corpus callosum, capsula interna ($p<0.05$). The fractional anisotropy value was higher in nucleus caudatus, putamen and a significant difference was observed ($p<0.05$).

Conclusion: The increase of axial diffusivity and mean diffusivity values axonal degeneration and demyelination of frontal, parietal, temporal, occipital, corpus callosum, white matter, limbic, subcortical structures; increased radial diffusivity values dysmyelination of the corpus callosum and capsula interna; fractional anisotropy increased values in nucleus caudatus and putamen may indicate a degenerative process, axon loss and inflammation.

Keywords: Huntington disease, neurodegenerative disease, brain, magnetic resonance imaging

INTRODUCTION

Huntington's Disease (HD) is an inherited neurodegenerative illness lead to unusual enlargement of CAG (Cytosine-Adenine-Guanine) repetitions in the IT15 gene above chromosome (1). More than 36 CAG repetitions, particularly in the striatum, can cause brain atrophy and neuronal death. The main clinical characteristics of HD contain psychiatric disorders, cognitive disturbance and motor dysfunction (2). The basic pathology of HD is reduction of projection neurons, which can cause microstructural alterations or white matter abnormality in the striatum (3). Most of neuroimaging study in HD has focused on identifying biomarkers of disease course and brain imaging has helped explain the pathology in HD. Diffusion Tensor Imaging (DTI) is a process that shows

the direction of limitation of diffusion in tissue, which can also be expressed quantitatively. By measuring diffusion parameters such as axial diffusivity (AD), mean diffusivity (MD), radial diffusivity (RD) and fractional anisotropy (FA) via DTI, the direction and entirety of white matter tracts and also gray matter microstructure can be revealed (4,5). DTI works on HD indicated that psychiatric, cognitive signs of HD cases were related to impaired striatal structures like cortico-striatal circuits. Müller et al. stated that remarkable increase in FA value in subcortical nuclei in the patient group in terms of control group (6). Studies noticed that an increment FA worths in the putamen and nucleus caudate (7). Andica et al. stated that an increment in MD values and a decline in FA values in the nucleus caudatus in both HD patients and Pre-symptomatic (PreHD) patients

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in comparison to controls. They also found a significant increment in AD and RD in corpus callosum in HD patients by comparison to controls. They also found a decline in FA worths in corpus callosum in preHD and HD by comparison to controls (8). Muhlau et al. realized that MD increment and FA decline in corpus callosum in the patient group in terms of control group (9). Zhang et al. found an increase RD, MD and AD values increased in capsula interna and capsula externa in the PreHD group than the control (10). Saba et al. realised that a remarkable decline in FA in the HD group in the corona radiata, corpus callosum, capsula externa, fasciculus longitudinalis superior and inferior, fasciculus frontooccipitalis compared to the control and preHD groups. They stated that the decrease in FA is an indicator of a degenerative process and axonal loss (11).

The aim of the study was to analyze each region of the brain in Huntington's patients using the brain parcellation method and to examine the effect of DTI parameters in these regions.

MATERIAL AND METHOD

This study applied with the ratification of Erciyes University School of Medicine Clinical Research Ethics Committee dated 25.09.2019, decision number 2019/643. A control group of 8 people and 8 Huntington's patients participated in the study. The control group contained in the study consisted of men and women who did not have any neurological disease, had normal brain imaging, and were older than 18 years of age. The patient group joined in the study consisted of men and women who were diagnosed with Huntington's disease confirmed by genetic testing (with 40 or more CAG repeats) and who did not have any neurological disease other than Huntington's disease clinically and were aged 32-60 years (Table 1). DTI were obtained by obtaining the consents of the control and patient groups included in the study.

Table 1. Demographic data of patient group

Patient number	Gender	Age	CAG repeat	Disease duration
1	F	32	68	11 years
2	F	61	40	7 years
3	F	44	43	5 years
4	F	39	51	4 years
5	M	53	43	9 years
6	M	52	49	9 years
7	M	51	42	4 years
8	M	60	42	6 years

CAG: sitozin-adenin-guanin

In the study, FA, MD, RD, AD parameters were calculated by making brain parcellation on DTI for the control and patient groups.

Sample

The specimen of this work was defined by power analysis.

Based on the calculation using the G*power 3.1 program. The sample dimension was stated as 16 (8 for each group) with an effect size of 1.4 a margin of error of 0.05, a confidence level of 0.80 and a population representation of 0.95 (12).

Diffusion Tensor Imaging Protocol

The DTI protocol used in the study consists of the following sequences:

- High resolution T1-weighted MPRAGE sequence to show the anatomical structure:** sagittal, Echo Time (TE)=2.67ms, Repetition time (TR)=1900ms, Matrix: 256x256, FOV=250mm, Slice Thickness=1mm.
- DTI:** axial, TR=3500ms, TE=83ms, number of sections=20, FOV=230mm, matrix: 128x128, section thickness=5mm, averages=3, b=0.1000 s/mm², 20 diffusion directions.

In this study, we used MriStudio (<http://www.MriStudio.org>), an image processing system. The MR images were automatically segmented and postprocessed through MRICloud [www.MRICloud.org] (13-15). Mricloud is a public web-based service for multi-contrast imaging segmentation and quantification. The DTI segmentation involved image mapping based upon a set of linear algorithms and Large Deformation Diffeomorphic Mapping anisotropy, and eigen vector such as fiber orientation, and a final step of multi-atlas labeling fusion (16-18). The trace is expressed as the sum of the eigenvalues ($\lambda_1+\lambda_2+\lambda_3$) and the mean diffusivity is their mean ($=\text{trace}/3$). Eigenvalue1 (λ_1) gives axial diffusivity. RD take the average of $\lambda_2+\lambda_3$. The index of the amount of diffusion asymmetry in the voxel ranging from 0 to 1 is defined as FA (19,20) (Figures 1 and 2) Maps were evaluated.

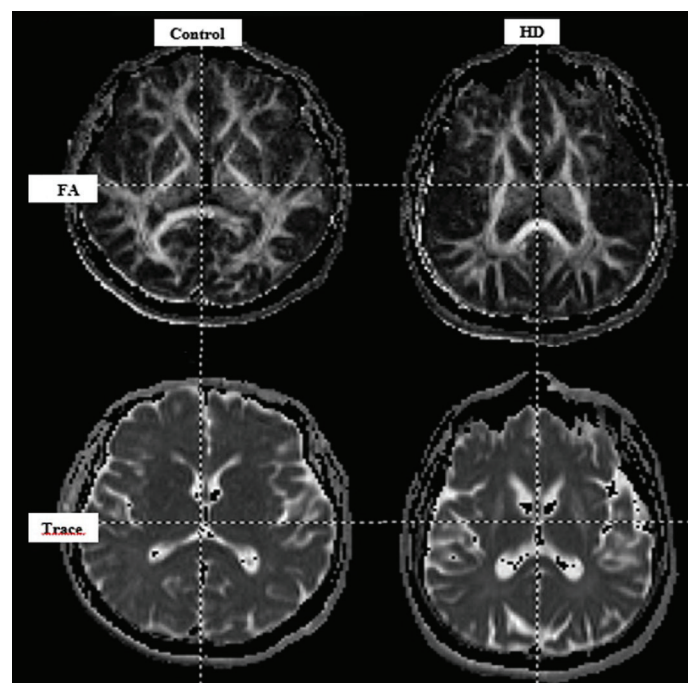


Figure 1. FA and MD maps in HD and control groups. FA: fractional anisotropy, MD: mean diffusivity, HD: Huntington's disease

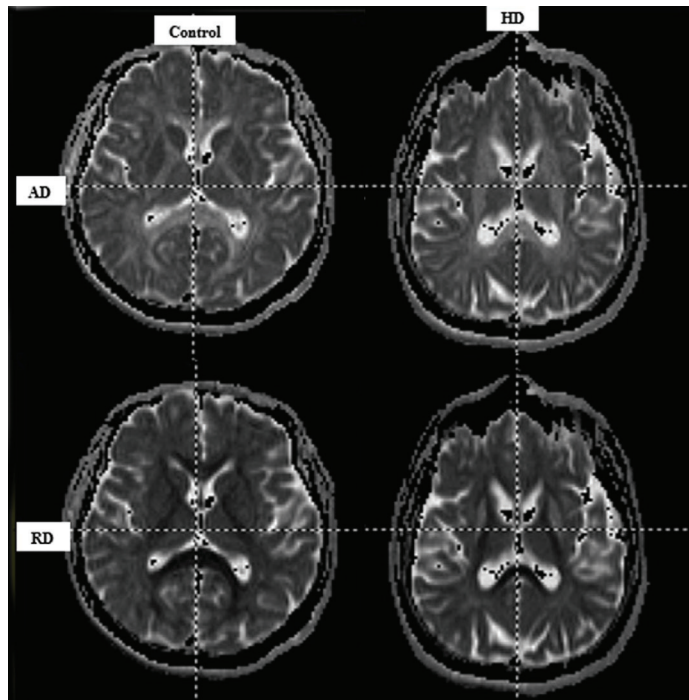


Figure 2. AD, and RD maps in HD and control groups. AD: axial diffusivity, RD: radial diffusivity. HD: Huntington's disease

The following regions of interest (ROI) were automatically segmented and considered in further analysis: cerebral lobes (frontal, parietal, temporal, occipital and limbic), putamen, caudate nucleus, globus pallidus, thalamus, corpus callosum. In addition, the diffusion parameters (AD, MD, FA and RD) of each structure in the brain were calculated by making brain parcellation with mricloud (<https://braingps.mricloud.org/>).

Subdivision mapping for DTI

1. DTIstudio was opened. DTI mapping from the file and whichever machine the image was taken from (Siemens, Philips etc.) was selected and automatic image registration and linear transformation were performed. After the process was completed, it was recorded in hdr format as FA, RD, ColorMap, MeanBO, Trace, Eigen Values and EigenVector.
2. ROleditor was opened. Then, statistical results of images such as FA, MD were obtained. MeanBO, FA and Trace images were recorded in hdr format as masked (21).

Statistical analysis

The analysis of the datum contain in the work was made with the Statistics Program in Social Sciences (SPSS) 25 program. Shapiro Wilks Test was used to control whether the datum contain in the study fit the normal dispersion. The signification grade (p) for the comparison tests was determined as 0.05. Since the mutables did not posses a normal dispersion ($p > 0.05$), the analysis was proceed with the non-parametric test method.

RESULTS

The number of females and males of the patient (8) and control (8) groups included in the study was equal. Average

age; While it was 44 for women in the patient group, it was found to be 54 for men. The mean age of women in the control group was 56.5 and men 44.75.

AD, MD, RD and FA parameters of the brain regions were calculated individually by DT imaging in the control and patient groups (Tables 2-6).

For AD; SFG ($p=0.001$), MFG ($p=0.001$), IFG ($p=0.001$), PrCG ($p=0.002$), LFOG ($p=0.001$), MFOG ($p=0.007$), RG ($p=0.001$), SPG ($p=0.002$), PoCG ($p=0.003$), AG ($p=0.005$), PrCu ($p=0.002$), SMG ($p=0.001$), Cu ($p=0.001$), LG ($p=0.001$), SOG ($p=0.001$), IOG ($p=0.001$), MOG ($p=0.001$), FuG ($p=0.001$), ENT ($p=0.006$), STG ($p=0.002$), ITG ($p=0.001$), MTG ($p=0.001$). A statistical important dissimilarity was found through the groups (control and patient) (Table 2). For MD; SFG ($p=0.001$), MFG ($p=0.001$), IFG ($p=0.001$), PrCG ($p=0.001$), LFOG ($p=0.001$), MFOG ($p=0.014$), RG ($p=0.001$), SPG ($p=0.001$), PoCG ($p=0.002$), AG ($p=0.002$), PrCu ($p=0.002$), SMG ($p=0.001$), Cu ($p=0.001$), LG ($p=0.001$), SOG ($p=0.001$), IOG ($p=0.001$), MOG ($p=0.001$), FuG ($p=0.001$), ENT ($p=0.006$), STG ($p=0.002$), ITG ($p=0.001$), MTG ($p=0.001$) = 0.001, a statistical important dissimilarity was found through the groups (control and patient) (Table 2). For RD; SFG ($p=0.012$), MFG ($p=0.012$), IFG ($p=0.012$), PrCG ($p=0.016$), LFOG ($p=0.012$), RG ($p=0.016$), SPG ($p=0.012$), PoCG ($p=0.016$), AG ($p=0.021$), PrCu ($p=0.027$), SMG ($p=0.012$), Cu ($p=0.012$), LG ($p=0.012$), SOG ($p=0.012$), IOG ($p=0.012$), MOG ($p=0.012$), FuG ($p=0.012$), STG ($p=0.021$), ITG ($p=0.016$), MTG ($p=0.012$) a statistical important through the groups (patient and control) in measures dissimilarity was found (Table 2). There was no statistical important dissimilarity through the groups (patient and control) in FA measures ($p > 0.05$) (Table 2).

For AD; A statistical meaningful dissimilarity was found through the groups (patient and control) in GCC ($p=0.001$), SCC ($p=0.001$) measures (Table 3). For MD; A statistically meaningful dissimilarity was found between the groups (patient and control) in GCC ($p=0.001$), BCC ($p=0.009$), SCC ($p=0.001$) measurements (Table 3). For RD; A statistical meaningful dissimilarity was found through the groups (patient and control) in GCC ($p=0.009$) and SCC ($p=0.009$) measures (Table 3). There was no statistical important dissimilarity through the groups (patient and control) in FA measures ($p > 0.05$) (Table 3).

For AD; CingG ($p=0.001$), Ins ($p=0.002$), Amyg ($p=0.001$), Hippo ($p=0.002$), FxST ($p=0.003$), H ($p=0.003$), NIM ($p=0.018$). A statistical significant dissimilarity was found through groups (patient and control) (Table 4). For MD; CingG ($p=0.001$), PHG ($p=0.045$), Ins ($p=0.002$), Amyg ($p=0.002$), Hippo ($p=0.002$), FxST ($p=0.005$), H ($p=0.002$), NIM ($p=0.016$). A statistical significant dissimilarity was found through the groups (patient and control) in measurements (Table 4). For RD; CingG ($p=0.012$), PHG ($p=0.018$), Ins ($p=0.027$), Amyg ($p=0.027$), Hippo ($p=0.021$), FxST ($p=0.027$), H ($p=0.012$). A statistical important difference was found through the groups (patient and control) (Table 4). No statistical important dissimilarity through the groups (patient and control) in FA measures ($p > 0.05$) (Table 4).

Table 2. AD, MD, RD, FA values of the structures in the frontal, parietal, occipital, temporal lobes

Variables	Groups	AD			MD			RD			FA		
		Mean±sd	M (Min-Max)	p value	Mean±sd	M (Mi-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value
SFG	Patient	1.21±0.07	1.23 (1.11-1.32)	0.001*	1.01±0.06	1.02 (0.93-1.1)	0.001*	0.81±0.24	0.89 (0.23-0.96)	0.012*	0.22±0.02	0.22 (0.2-0.26)	0.674
	Control	1.03±0.05	1.02 (0.96-1.1)		0.85±0.04	0.84 (0.78-0.92)		0.76±0.04	0.75 (0.7-0.83)		0.21±0.04	0.23 (0.15-0.24)	
MFG	Patient	1.29±0.08	1.31 (1.18-1.4)	0.001*	1.1±0.07	1.11 (1.01-1.19)	0.001*	0.9±0.29	0.99 (0.2-1.08)	0.012*	0.19±0.01	0.19 (0.18-0.22)	0.834
	Control	1.09±0.05	1.08 (1.03-1.16)		0.92±0.04	0.91 (0.87-0.98)		0.83±0.04	0.82 (0.79-0.89)		0.19±0.03	0.2 (0.14-0.22)	
IFG	Patient	1.25±0.06	1.25 (1.16-1.33)	0.001*	1.05±0.06	1.04 (0.97-1.13)	0.001*	0.85±0.26	0.92 (0.21-1.03)	0.012*	0.21±0.01	0.21 (0.2-0.24)	0.141
	Control	1.06±0.05	1.05 (1.01-1.15)		0.87±0.05	0.85 (0.82-0.96)		0.77±0.05	0.75 (0.72-0.86)		0.21±0.04	0.24 (0.14-0.25)	
PrCG	Patient	1.15±0.05	1.15 (1.09-1.22)	0.002*	0.91±0.04	0.9 (0.86-0.98)	0.001*	0.72±0.18	0.77 (0.28-0.85)	0.016*	0.27±0.02	0.27 (0.24-0.32)	0.401
	Control	1.03±0.04	1.03 (0.98-1.1)		0.79±0.04	0.79 (0.75-0.86)		0.67±0.04	0.67 (0.64-0.74)		0.26±0.06	0.29 (0.17-0.31)	
LFOG	Patient	1.27±0.05	1.28 (1.2-1.34)	0.001*	1.09±0.05	1.07 (1.04-1.17)	0.001*	0.89±0.3	0.97 (0.17-1.08)	0.012*	0.18±0.02	0.17 (0.16-0.22)	0.636
	Control	1.1±0.05	1.1 (1.04-1.19)		0.92±0.05	0.92 (0.87-1.02)		0.84±0.05	0.84 (0.79-0.93)		0.17±0.04	0.19 (0.1-0.2)	
MFOG	Patient	1.27±0.06	1.26 (1.2-1.36)	0.007*	1.09±0.05	1.07 (1.03-1.17)	0.014*	0.89±0.3	0.97 (0.16-1.08)	0.141	0.17±0.03	0.16 (0.15-0.24)	0.916
	Control	1.14±0.07	1.11 (1.07-1.27)		0.98±0.07	0.95 (0.91-1.1)		0.9±0.07	0.87 (0.84-1.02)		0.15±0.04	0.17 (0.09-0.18)	
RG	Patient	1.22±0.04	1.21 (1.16-1.28)	0.001*	1.06±0.04	1.06 (1.02-1.14)	0.001*	0.87±0.3	0.97 (0.13-1.03)	0.016*	0.15±0.02	0.15 (0.13-0.19)	0.753
	Control	1.07±0.06	1.07 (0.98-1.18)		0.93±0.06	0.93 (0.85-1.03)		0.86±0.05	0.87 (0.78-0.96)		0.14±0.03	0.16 (0.09-0.17)	
SPG	Patient	1.33±0.07	1.35 (1.23-1.43)	0.002*	1.08±0.06	1.1 (0.99-1.17)	0.001*	0.86±0.25	0.94 (0.26-0.99)	0.012*	0.26±0.02	0.25 (0.23-0.3)	0.208
	Control	1.15±0.06	1.15 (1.07-1.24)		0.9±0.05	0.9 (0.84-0.99)		0.78±0.05	0.77 (0.72-0.86)		0.26±0.05	0.28 (0.17-0.3)	
PoCG	Patient	1.42±0.11	1.46 (1.24-1.53)	0.003*	1.22±0.1	1.26 (1.08-1.32)	0.002*	1±0.34	1.09 (0.19-1.23)	0.016*	0.19±0.02	0.19 (0.16-0.23)	0.916
	Control	1.18±0.08	1.16 (1.08-1.28)		1.01±0.07	0.98 (0.92-1.1)		0.92±0.07	0.89 (0.84-1.02)		0.18±0.03	0.19 (0.14-0.21)	
AG	Patient	1.41±0.11	1.43 (1.24-1.52)	0.005*	1.21±0.1	1.24 (1.07-1.32)	0.002*	0.99±0.33	1.09 (0.19-1.22)	0.021*	0.18±0.02	0.18 (0.16-0.22)	0.462
	Control	1.18±0.07	1.16 (1.08-1.28)		1±0.07	0.98 (0.91-1.09)		0.91±0.07	0.89 (0.82-0.99)		0.18±0.03	0.19 (0.13-0.2)	
PrCu	Patient	1.46±0.12	1.45 (1.28-1.6)	0.002*	1.29±0.11	1.29 (1.14-1.43)	0.002*	1.06±0.38	1.15 (0.14-1.32)	0.027*	0.15±0.01	0.15 (0.14-0.16)	0.834
	Control	1.2±0.08	1.18 (1.12-1.32)		1.06±0.07	1.04 (0.98-1.17)		0.99±0.07	0.97 (0.91-1.1)		0.14±0.03	0.15 (0.09-0.16)	
SMG	Patient	1.33±0.08	1.33 (1.22-1.45)	0.001*	1.15±0.07	1.15 (1.07-1.26)	0.001*	0.93±0.31	1.02 (0.18-1.11)	0.012*	0.18±0.02	0.18 (0.15-0.22)	0.294
	Control	1.12±0.07	1.11 (1.05-1.24)		0.95±0.06	0.94 (0.87-1.05)		0.86±0.06	0.85 (0.79-0.96)		0.18±0.03	0.2 (0.13-0.2)	
Cu	Patient	1.41±0.08	1.43 (1.32-1.52)	0.001*	1.24±0.08	1.25 (1.12-1.34)	0.001*	1.03±0.36	1.16 (0.16-1.25)	0.012*	0.16±0.02	0.16 (0.13-0.2)	0.248
	Control	1.15±0.06	1.17 (1.03-1.23)		0.98±0.05	0.98 (0.88-1.05)		0.89±0.05	0.89 (0.8-0.96)		0.17±0.04	0.18 (0.1-0.2)	

sd: standard deviation, M: median, p: Mann Whitney U test significance value. *p<0.05; there is a statistically significant difference between the groups. SFG: gyrus frontalis superior, MFG: gyrus frontalis medius, IFG: gyrus frontalis inferior, Pr: CG: gyrus precentralis, LFOG: gyrus fronto-orbitalis lateralis, MFOG: gyrus fronto-orbitalis medius, RG: gyrus rectus, SPG: lobulus parietalis superior, Po: CG: gyrus postcentralis, AG: gyrus angularis, Pr: Cu: cuneus, LF: fasciculus lenticularis, SOG: gyri occipitalis superior, IOG: gyri occipitalis inferior, MOG: gyri occipitalis medius, FUG: gyrus fusiformis, ENT: cortex entorhinalis, STG: gyrus temporalis superior, ITG-: gyrus temporalis inferior, MTG: gyrus temporalis medius

Table 2. AD, MD, RD, FA values of the structures in the frontal, parietal, occipital, temporal lobes

LG	Patient	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value
LG	Patient	1.36±0.08	1.36 (1.25-1.48)	0.001*	1.18±0.08	1.18 (1.08-1.29)	0.001*	0.97±0.34	1.07 (0.15-1.19)	0.012*	0.16±0.02	0.16 (0.15-0.2)	0.012*	0.17±0.04	0.19 (0.11-0.2)	0.401
	Control	1.11±0.06	1.13 (1-1.19)		0.94±0.06	0.96 (0.85-1.03)		0.86±0.06	0.87 (0.77-0.95)		0.23±0.02	0.23 (0.21-0.27)	0.012*	0.23±0.04	0.24 (0.16-0.27)	0.916
SOG	Patient	1.29±0.06	1.31 (1.21-1.38)	0.001*	1.06±0.06	1.07 (0.98-1.14)	0.001	0.86±0.26	0.92 (0.24-1.03)	0.012*	0.16±0.02	0.16 (0.14-0.22)	0.012*	0.17±0.04	0.19 (0.1-0.2)	0.294
	Control	1.11±0.08	1.12 (0.96-1.2)		0.89±0.07	0.9 (0.77-0.97)		0.91±0.31	0.98 (0.16-1.12)	0.012*	0.23±0.04	0.24 (0.16-0.27)		0.23±0.04	0.24 (0.16-0.27)	
IOG	Patient	1.27±0.07	1.29 (1.17-1.38)	0.001*	1.1±0.06	1.09 (1.03-1.21)	0.001*	0.81±0.06	0.82 (0.71-0.9)	0.012*	0.16±0.02	0.16 (0.14-0.22)	0.012*	0.17±0.04	0.19 (0.1-0.2)	0.294
	Control	1.06±0.06	1.07 (0.96-1.15)		0.89±0.06	0.9 (0.8-0.98)		0.81±0.06	0.82 (0.71-0.9)		0.16±0.02	0.16 (0.14-0.22)		0.17±0.04	0.19 (0.1-0.2)	
MOG	Patient	1.36±0.09	1.36 (1.27-1.51)	0.001*	1.18±0.09	1.18 (1.06-1.32)	0.001*	0.98±0.33	1.07 (0.18-1.22)	0.012*	0.17±0.02	0.16 (0.15-0.21)	0.012*	0.17±0.02	0.16 (0.15-0.21)	0.345
	Control	1.1±0.06	1.1 (1.02-1.19)		0.93±0.05	0.93 (0.85-1.01)		0.84±0.05	0.84 (0.77-0.92)		0.17±0.02	0.16 (0.15-0.21)		0.17±0.04	0.19 (0.11-0.2)	
FuG	Patient	1.26±0.08	1.25 (1.16-1.42)	0.001*	1.08±0.07	1.07 (1-1.24)	0.001*	0.9±0.3	0.97 (0.17-1.15)	0.012*	0.17±0.02	0.17 (0.16-0.21)	0.012*	0.17±0.02	0.18 (0.1-0.2)	0.345
	Control	1.07±0.05	1.07 (0.99-1.13)		0.9±0.05	0.91 (0.82-0.97)		0.82±0.05	0.83 (0.74-0.89)		0.17±0.02	0.17 (0.16-0.21)		0.17±0.04	0.18 (0.1-0.2)	
ENT	Patient	1.41±0.26	1.47 (1.03-1.67)	0.006*	1.2±0.23	1.24 (0.87-1.45)	0.006*	0.98±0.39	1.07 (0.17-1.34)	0.052	0.17±0.02	0.18 (0.14-0.21)		0.15±0.06	0.18 (0.05-0.19)	0.834
	Control	1.04±0.09	1.02 (0.94-1.19)		0.88±0.08	0.86 (0.78-1)		0.79±0.07	0.78 (0.69-0.91)		0.17±0.02	0.18 (0.14-0.21)		0.15±0.06	0.18 (0.05-0.19)	
STG	Patient	1.38±0.09	1.41 (1.24-1.48)	0.002*	1.19±0.08	1.21 (1.08-1.29)	0.002*	0.98±0.33	1.08 (0.17-1.19)	0.021*	0.17±0.01	0.17 (0.16-0.2)	0.021*	0.17±0.03	0.19 (0.12-0.19)	0.294
	Control	1.15±0.08	1.15 (1.04-1.28)		0.98±0.07	0.98 (0.88-1.11)		0.9±0.07	0.9 (0.8-1.02)		0.17±0.01	0.17 (0.16-0.2)		0.17±0.03	0.19 (0.12-0.19)	
ITG	Patient	1.19±0.06	1.2 (1.1-1.26)	0.001*	1±0.05	1 (0.92-1.06)	0.001*	0.81±0.25	0.89 (0.19-0.96)	0.016*	0.2±0.02	0.2 (0.19-0.24)	0.016*	0.18±0.05	0.2 (0.1-0.23)	0.401
	Control	1.07±0.02	1.2 (1.04-1.1)		0.89±0.03	1 (0.84-0.93)		0.79±0.03	0.89 (0.75-0.84)		0.2±0.02	0.2 (0.19-0.24)		0.18±0.05	0.2 (0.1-0.23)	
MTG	Patient	1.21±0.05	1.06 (1.14-1.27)	0.001*	1.03±0.04	0.88 (0.98-1.09)	0.001*	0.85±0.27	0.79 (0.18-1)	0.012*	0.18±0.02	0.21 (0.16-0.21)	0.012*	0.18±0.02	0.21 (0.16-0.21)	0.345
	Control	1.02±0.18	1.22 (0.57-1.14)		0.9±0.04	1.04 (0.84-0.97)		0.82±0.04	0.92 (0.75-0.88)		0.18±0.02	0.21 (0.16-0.21)		0.17±0.04	0.18 (0.11-0.2)	

sd: standard deviation, M: median, p: Mann Whitney U test significance value. *p<0.05; there is a statistically significant difference between the groups. SFG: gyrus frontalis superior, MFG: gyrus frontalis medius, IFG: gyrus frontalis inferior, Pr. CG: gyrus precentralis, LFOG: gyrus frontoorbitalis lateralis, MFOG: gyrus frontoorbitalis medius, RG: gyrus rectus, SPG: lobulus parietalis superior, Po. CG: gyrus postcentralis, AG: gyrus angularis, Pr. Cu: cuneus, SMG: gyrus supramarginalis, Cu: cuneus, LF: fasciculus lenticularis, SOG: gyri occipitalis superior, IOG: gyri occipitalis inferior, MOG: gyri occipitalis medius, FUG: gyrus fusiformis, ENT: cortex entorhinalis, STG: gyrus temporalis superior, ITG: gyrus temporalis inferior, MTG: gyrus temporalis medius

Table 3. AD, MD, RD, FA values of structures in corpus callosum

Variables	Groups	AD			MD			RD			FA					
		Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value			
GCC	Patient	1.71±0.06	1.71 (1.64-1.79)	0.001*	1.09±0.08	1.08 (1.01-1.22)	0.001*	0.75±0.13	0.73 (0.51-0.94)	0.009*	0.49±0.03	0.51 (0.44-0.53)	0.009*	0.48±0.17	0.55 (0.2-0.61)	0.093
	Control	1.57±0.05	1.59 (1.5-1.62)		0.93±0.05	0.93 (0.84-0.97)		0.6±0.05	0.62 (0.51-0.65)		0.47±0.03	0.47 (0.44-0.53)		0.47±0.03	0.47 (0.44-0.53)	0.401
BCC	Patient	1.66±0.07	1.64 (1.56-1.8)	0.059	1.06±0.05	1.05 (1-1.12)	0.009*	0.72±0.11	0.75 (0.46-0.83)	0.115	0.47±0.03	0.47 (0.44-0.53)	0.115	0.43±0.16	0.5 (0.17-0.56)	0.401
	Control	1.58±0.07	1.6 (1.45-1.64)		0.98±0.05	0.99 (0.92-1.06)		0.68±0.05	0.67 (0.63-0.77)		0.47±0.03	0.47 (0.44-0.53)		0.43±0.16	0.5 (0.17-0.56)	
SCC	Patient	1.73±0.03	1.72 (1.69-1.8)	0.001*	1.05±0.04	1.04 (1-1.12)	0.001*	0.69±0.08	0.7 (0.54-0.8)	0.009*	0.53±0.02	0.53 (0.48-0.56)	0.009*	0.49±0.17	0.58 (0.21-0.62)	0.093
	Control	1.6±0.06	1.59 (1.5-1.7)		0.92±0.05	0.91 (0.86-0.99)		0.58±0.04	0.57 (0.53-0.64)		0.49±0.17	0.58 (0.21-0.62)		0.49±0.17	0.58 (0.21-0.62)	

sd: standard deviation, M: median, p: Mann Whitney U test significance value. *p<0.05; there is a statistically significant difference between the groups. GCC: genu corporis callosi, BCC: truncus corporis callosi, SCC: splenium corporis callosi, CGC: genu corporis callosi, GCC: genu corporis callosi, BCC: truncus corporis callosi, SCC: splenium corporis callosi

Table 4. AD, MD, RD, FA values of structures in the limbic lobe

Variables	Groups	AD			MD			RD			FA		
		Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value
CingG	Patient	1.25±0.06	1.24 (1.18-1.34)	0.001*	1.09±0.05	1.08 (1.03-1.17)	0.001*	1.01±0.05	1.01 (0.96-1.09)	0.012*	0.16±0.01	0.16 (0.15-0.19)	0.529
	Control	1.05±0.05	1.04 (1-1.13)		0.9±0.04	0.89 (0.86-0.98)		0.83±0.04	0.81 (0.78-0.9)		0.16±0.03	0.17 (0.11-0.17)	
PHG	Patient	1.83±0.4	1.79 (1.33-2.31)	0.068	1.58±0.36	1.57 (1.15-2.08)	0.045*	1.45±0.34	1.46 (1.06-1.95)	0.018*	0.17±0.04	0.17 (0.13-0.23)	0.201
	Control	1.43±0.15	1.42 (1.27-1.65)		1.18±0.14	1.17 (1.01-1.38)		1.03±0.13	1.04 (0.88-1.25)		0.2±0.06	0.21 (0.09-0.24)	
Ins	Patient	1.29±0.09	1.25 (1.21-1.42)	0.002*	1.11±0.07	1.08 (1.05-1.21)	0.002*	1.03±0.06	0.99 (0.97-1.11)	0.027*	0.17±0.01	0.16 (0.16-0.18)	0.674
	Control	1.09±0.04	1.1 (1.04-1.15)		0.93±0.04	0.94 (0.88-0.99)		0.85±0.04	0.85 (0.81-0.91)		0.16±0.04	0.17 (0.09-0.18)	
Amyg	Patient	1.22±0.02	1.21 (1.19-1.25)	0.001*	1.02±0.03	1.01 (0.99-1.06)	0.002*	0.92±0.04	0.91 (0.87-0.96)	0.027*	0.19±0.03	0.19 (0.16-0.24)	0.674
	Control	1.07±0.03	1.08 (1.02-1.1)		0.88±0.03	0.9 (0.84-0.91)		0.79±0.03	0.81 (0.75-0.82)		0.18±0.05	0.2 (0.08-0.2)	
Hippo	Patient	1.5±0.08	1.54 (1.4-1.58)	0.002*	1.25±0.07	1.26 (1.17-1.34)	0.002*	1.13±0.07	1.12 (1.06-1.22)	0.021*	0.19±0.02	0.18 (0.18-0.22)	0.401
	Control	1.22±0.09	1.2 (1.11-1.35)		1±0.08	0.98 (0.91-1.12)		0.89±0.08	0.87 (0.81-1)		0.19±0.04	0.21 (0.11-0.22)	
FxFST	Patient	1.58±0.07	1.58 (1.5-1.68)	0.003*	1.1±0.03	1.09 (1.08-1.14)	0.005*	0.86±0.04	0.87 (0.82-0.91)	0.027*	0.39±0.03	0.41 (0.34-0.42)	0.674
	Control	1.4±0.1	1.41 (1.27-1.52)		0.92±0.06	0.93 (0.82-0.99)		0.68±0.05	0.69 (0.6-0.74)		0.39±0.13	0.43 (0.12-0.46)	
Fx	Patient	2.36±0.27	2.45 (1.88-2.52)	0.115	1.65±0.37	1.76 (1.01-1.91)	0.059	1.4±0.55	1.41 (0.57-2.07)	0.294	0.42±0.14	0.38 (0.3-0.65)	0.294
	Control	2.23±0.31	2.25 (1.77-2.57)		1.47±0.33	1.54 (1.03-1.82)		1.1±0.36	1.12 (0.66-1.58)		0.45±0.17	0.51 (0.13-0.58)	
H	Patient	1.52±0.15	1.45 (1.36-1.71)	0.003*	1.19±0.09	1.15 (1.12-1.34)	0.002*	1.03±0.07	1 (0.96-1.15)	0.012*	0.27±0.04	0.27 (0.21-0.31)	0.172
	Control	1.08±0.28	1.12 (0.59-1.44)		0.9±0.11	0.86 (0.81-1.1)		0.77±0.1	0.74 (0.68-0.93)		0.24±0.09	0.26 (0.08-0.32)	
NIM	Patient	1.1±0.05	1.09 (1.05-1.17)	0.018*	0.88±0.03	0.88 (0.82-0.91)	0.016*	0.76±0.04	0.77 (0.71-0.8)	0.093	0.25±0.05	0.23 (0.21-0.32)	0.529
	Control	1.02±0.04	1.03 (0.94-1.05)		0.77±0.02	0.77 (0.73-0.79)		0.65±0.02	0.64 (0.62-0.68)		0.27±0.07	0.28 (0.14-0.32)	

sd: standard deviation, M: median, p: Mann Whitney U test significance value, *p<0.05; there is a statistically significant difference between the groups. CingG: gyrus cinguli, PHG: gyrus parahippocampalis, Ins: insula, Amyg: amygdala, Hippo: hippocampus, Fx/ST: fornix-stria terminalis, Fx: fornix, H: hypothalamus, NIM: nucleus innominata

Table 5. AD, MD, RD, FA values of fascicles found in white matter

Variables	Groups	AD			MD			RD			FA		
		Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value
SLF	Patient	1.16±0.04	1.18 (1.1-1.19)	0.001*	0.83±0.03	0.85 (0.78-0.87)	0.001*	0.63±0.11	0.67 (0.36-0.72)	0.016*	0.36±0.01	0.36 (0.34-0.38)	0.172
	Control	1.04±0.03	1.05 (0.99-1.07)		0.74±0.03	0.74 (0.7-0.78)		0.59±0.03	0.58 (0.55-0.63)		0.32±0.13	0.38 (0.11-0.4)	
IFO	Patient	1.26±0.04	1.25 (1.2-1.33)	0.001*	0.87±0.03	0.88 (0.84-0.92)	0.001*	0.65±0.11	0.69 (0.38-0.72)	0.012*	0.39±0.02	0.38 (0.37-0.42)	1.000
	Control	1.16±0.04	1.17 (1.08-1.19)		0.78±0.03	0.78 (0.73-0.81)		0.59±0.03	0.59 (0.55-0.63)		0.34±0.12	0.4 (0.15-0.44)	
UNC	Patient	1.28±0.06	1.25 (1.2-1.38)	0.016*	0.93±0.04	0.92 (0.88-1.02)	0.001*	0.7±0.15	0.75 (0.33-0.78)	0.024*	0.34±0.03	0.33 (0.3-0.37)	0.753
	Control	1.2±0.04	1.18 (1.16-1.25)		0.85±0.03	0.84 (0.82-0.88)		0.67±0.03	0.66 (0.64-0.72)		0.3±0.11	0.36 (0.12-0.39)	
SS	Patient	1.36±0.05	1.36 (1.29-1.45)	0.001*	0.96±0.04	0.97 (0.88-1.01)	0.002*	0.72±0.14	0.78 (0.39-0.79)	0.021*	0.38±0.02	0.39 (0.35-0.42)	0.294
	Control	1.24±0.05	1.25 (1.16-1.32)		0.84±0.05	0.83 (0.78-0.93)		0.64±0.06	0.63 (0.58-0.73)		0.35±0.14	0.43 (0.12-0.44)	

sd: standard deviation, M: Median, p: Mann Whitney U test significance value, *p<0.05; there is a statistically significant difference between the groups. SLF: sacculus longitudinalis superior IFO: fasciculus frontooccipitalis inferior UNC: fasciculus uncinatus SS: sagittal stratum ACR: anterior corona radiata SCR: superior corona radiata PCR: posterior corona radiata

Table 5. AD, MD, RD, FA values of fascicles found in white matter

ACR	Patient	1.22±0.03	1.22 (1.17-1.27)	0.001*	0.85±0.03	0.85 (0.81-0.91)	0.001*	0.64±0.1	0.65 (0.4-0.74)	0.012*	0.39±0.03	0.39 (0.34-0.42)	0.753
Control		1.1±0.03	1.1 (1.05-1.14)		0.75±0.03	0.76 (0.7-0.79)		0.58±0.03	0.58 (0.52-0.62)		0.34±0.13	0.39 (0.12-0.43)	
SCR	Patient	1.17±0.03	1.18 (1.11-1.19)	0.001*	0.79±0.03	0.8 (0.75-0.84)	0.001*	0.58±0.08	0.59 (0.42-0.67)	0.021*	0.41±0.03	0.42 (0.36-0.47)	0.916
Control		1.06±0.04	1.07 (1-1.11)		0.71±0.03	0.72 (0.68-0.75)		0.54±0.02	0.54 (0.5-0.57)		0.35±0.14	0.42 (0.13-0.45)	
PCR	Patient	1.28±0.06	1.27 (1.18-1.37)	0.002*	0.86±0.04	0.86 (0.81-0.91)	0.001*	0.63±0.09	0.65 (0.43-0.7)	0.046*	0.42±0.03	0.42 (0.39-0.47)	0.208
Control		1.13±0.05	1.12 (1.08-1.22)		0.76±0.04	0.76 (0.72-0.81)		0.58±0.03	0.58 (0.55-0.63)		0.35±0.14	0.42 (0.12-0.44)	

sd: standard deviation, M: Median, p: Mann Whitney U test significance value, *p<0.05; there is a statistically significant difference between the groups. SLF: sacculus longitudinalis superior IFO: fasciculus frontooccipitalis inferior UNC: fasciculus uncinatus SS: sagittal stratum ACR: anterior corona radiata SCR: superior corona radiata PCR: posterior corona radiata

Table 6. AD, MD, RD, FA values of structures in the subcortical region

Variables	Groups	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value	Mean±sd	M (Min-Max)	p value						
				AD				MD				RD				FA			
ALIC	Patient	1.36±0.07	1.32 (1.28-1.46)	0.001*	0.86±0.06	0.83 (0.8-0.94)	0.001*	0.6±0.07	0.6 (0.5-0.67)	0.003*	0.49±0.03	0.48 (0.45-0.52)	0.003*	0.674					
	Control	1.16±0.04	1.15 (1.1-1.21)		0.72±0.02	0.72 (0.69-0.73)		0.49±0.01	0.49 (0.47-0.51)		0.5±0.02	0.49 (0.48-0.52)							
PLIC	Patient	1.41±0.03	1.41 (1.36-1.44)	0.001*	0.81±0.03	0.82 (0.77-0.84)	0.001*	0.53±0.05	0.54 (0.45-0.58)	0.012*	0.58±0.03	0.57 (0.55-0.63)	0.012*	0.753					
	Control	1.25±0.03	1.24 (1.22-1.31)		0.72±0.02	0.72 (0.69-0.74)		0.45±0.02	0.45 (0.43-0.48)		0.58±0.01	0.58 (0.55-0.59)							
RLIC	Patient	1.4±0.03	1.4 (1.38-1.45)	0.001*	0.89±0.03	0.91 (0.84-0.91)	0.001*	0.61±0.08	0.65 (0.48-0.67)	0.027*	0.48±0.03	0.48 (0.45-0.53)	0.027*	0.834					
	Control	1.22±0.03	1.22 (1.18-1.27)		0.77±0.02	0.77 (0.74-0.79)		0.55±0.02	0.54 (0.51-0.58)		0.49±0.02	0.49 (0.46-0.51)							
Snigra	Patient	1.43±0.59	1.3 (0.98-2.45)	0.584	0.97±0.48	0.78 (0.71-1.82)	1.000	0.69±0.47	0.58 (0.37-1.51)	0.715	0.44±0.15	0.39 (0.29-0.69)	0.465						
	Control	1.16±0.08	1.14 (1.08-1.3)		0.77±0.03	0.77 (0.74-0.8)		0.57±0.07	0.57 (0.46-0.65)		0.46±0.08	0.44 (0.38-0.6)							
Caud	Patient	1.4±0.16	1.36 (1.25-1.64)	0.001*	1.15±0.14	1.09 (1.02-1.36)	0.001*	0.88±0.37	0.94 (0.26-1.21)	0.01*2	0.24±0.02	0.23 (0.21-0.26)	0.005*						
	Control	0.98±0.03	0.97 (0.95-1.02)		0.81±0.02	0.81 (0.78-0.84)		0.73±0.02	0.73 (0.69-0.76)		0.21±0.01	0.2 (0.19-0.23)							
Put	Patient	1.21±0.07	1.16 (1.15-1.3)	0.001*	0.99±0.06	0.97 (0.91-1.05)	0.001*	0.74±0.3	0.87 (0.21-0.94)	0.012*	0.23±0.03	0.22 (0.19-0.26)	0.009*						
	Control	0.88±0.01	0.88 (0.86-0.9)		0.73±0.01	0.74 (0.71-0.75)		0.66±0.02	0.66 (0.64-0.68)		0.19±0.02	0.19 (0.17-0.22)							
GP	Patient	1.23±0.12	1.23 (1.12-1.42)	0.001*	0.97±0.09	0.97 (0.88-1.11)	0.001*	0.73±0.27	0.8 (0.28-0.95)	0.021*	0.25±0.02	0.24 (0.23-0.28)	0.674						
	Control	0.98±0.06	1.01 (0.86-1.02)		0.77±0.03	0.79 (0.72-0.8)		0.67±0.02	0.68 (0.64-0.69)		0.26±0.02	0.27 (0.22-0.27)							
NA	Patient	1.32±0.09	1.33 (1.18-1.43)	0.006*	1.1±0.08	1.13 (0.99-1.18)	0.005*	0.83±0.36	0.94 (0.19-1.06)	0.046*	0.2±0.02	0.19 (0.18-0.23)	0.834						
	Control	1.05±0.06	1.04 (0.96-1.13)		0.87±0.05	0.87 (0.8-0.95)		0.78±0.05	0.77 (0.71-0.86)		0.21±0.01	0.21 (0.19-0.23)							
Thal	Patient	1.39±0.11	1.38 (1.26-1.56)	0.002*	1.07±0.09	1.07 (0.96-1.19)	0.001*	0.78±0.28	0.87 (0.3-1.01)	0.016*	0.35±0.01	0.3 (0.28-0.32)	0.462						
	Control	1.18±0.05	1.16 (1.12-1.24)		0.88±0.05	0.87 (0.83-0.95)		0.73±0.05	0.72 (0.68-0.8)		0.32±0.01	0.32 (0.3-0.34)							
EC	Patient	1.14±0.03	1.15 (1.1-1.18)	0.001*	0.84±0.04	0.86 (0.78-0.87)	0.001*	0.62±0.16	0.71 (0.34-0.72)	0.027*	0.33±0.02	0.33 (0.31-0.37)	0.916						
	Control	1.02±0.03	1.02 (0.97-1.05)		0.73±0.02	0.73 (0.71-0.76)		0.59±0.02	0.58 (0.57-0.62)		0.36±0.02	0.36 (0.33-0.39)							
AL	Patient	1.4±0.12	1.4 (1.23-1.54)	0.059	1.08±0.1	1.06 (0.96-1.2)	0.046*	0.77±0.29	0.87 (0.27-0.98)	0.294	0.29±0.03	0.3 (0.27-0.33)	0.834						
	Control	1.27±0.11	1.29 (1.13-1.41)		0.96±0.1	0.94 (0.84-1.13)		0.81±0.1	0.77 (0.7-0.98)		0.31±0.04	0.31 (0.25-0.36)							
LF	Patient	1.5±0.12	1.54 (1.32-1.65)	0.345	1.03±0.12	1.04 (0.85-1.2)	0.141	0.72±0.21	0.79 (0.42-0.98)	0.345	0.41±0.04	0.42 (0.36-0.45)	0.600						
	Control	1.48±0.11	1.49 (1.3-1.63)		0.98±0.09	1 (0.82-1.09)		0.73±0.08	0.75 (0.58-0.82)		0.43±0.02	0.43 (0.41-0.46)							

sd: standard deviation, M: Median, p: Mann Whitney U test significance value, *p<0.05; there is a statistically significant difference between the groups. ALIC: Crus anterior capsula interna PLIC: Crus posterior capsula interna RLIC: Pars retrolentiformis Snigra: Substantia Nigra Caud: Nucleus Caudatus Put: Putamen GP: Globus Pallidus NA: Nucleus Accumbens Thal: Thalamus EC: Capsula Externa A: Ansa lenticularis LF: Fasciculus lenticularis

For AD; SLF ($p=0.001$), IFO ($p=0.001$), UNC ($p=0.016$), SS ($p=0.001$), ACR ($p=0.001$), SCR ($p=0.001$), PCR ($p=0.002$). A statistical significant dissimilarity was found through the groups (patient and control) (Table 5). for MD; SLF ($p=0.001$), IFO ($p=0.001$), UNC ($p=0.001$), SS ($p=0.002$), ACR ($p=0.001$), SCR ($p=0.001$), PCR ($p=0.001$). A statistical important dissimilarity was found through groups (patient and control) (Table 5). For RD; SLF ($p=0.016$), IFO ($p=0.012$), UNC ($p=0.024$), SS ($p=0.021$), ACR ($p=0.012$), SCR ($p=0.021$), PCR ($p=0.046$) A statistically important dissimilarity was found through the groups (patient and control) (Table 5). No statistical important dissimilarity through the groups (patient and control) in FA measures ($p>0.05$) (Table 5). For AD; ALIC ($p=0.001$), PLIC ($p=0.001$), RLIC ($p=0.001$), Caud ($p=0.001$), Put ($p=0.001$), GP ($p=0.001$), NA ($p=0.006$), Thal ($p=0.002$), EC ($p=0.001$) measures were statistical significant dissimilarity through groups (patient and control) (Table 6). For MD; ALIC ($p=0.001$), PLIC ($p=0.001$), RLIC ($p=0.001$), Caud ($p=0.001$), Put ($p=0.001$), GP ($p=0.001$), NA ($p=0.005$), Thal ($p=0.001$), EC ($p=0.001$), AL ($p=0.046$) measures were statistical important dissimilarity through groups (patient and control) (Table 6). For RD; ALIC ($p=0.003$), PLIC ($p=0.012$), RLIC ($p=0.027$), Caud ($p=0.012$), Put ($p=0.012$), GP ($p=0.021$), NA ($p=0.046$), Thal ($p=0.016$), EC ($p=0.027$) measurements were statistical significant dissimilarity through the groups (patient and control) (Table 6). For FA; A statistical significant dissimilarity was found through the groups (patient and control) in Caud ($p=0.005$) and Put ($p=0.009$) measurements (Table 6).

DISCUSSION

White matter degeneration is important in the progression of HD. DTI is widely used to reveal white matter microstructural alterations related with HD pathology (22). Ciarmiello et al. explained that the degeneration of the brain in HD affects both subcortical and cortical regions (23). The reducing in white matter volume might affect the reduction in the number of axons in the impressed area and the reduction in the quantity of myelin surrounding the axons. They stated that there may be a decrease in white matter volume before gray matter atrophy and this is related to neuronal dysfunction. Zhang et al. showed that reduced axonal density is one of the main factors underlying pre-HD white matter pathology (10). Matsui et al. observed an increase in RD and FA worths in the prefrontal white matter tracts in HD (24). Klöppel et al. realized that a decrease in connectivity among the frontal cortex and truncus corporis callosi in PreHD compared to control (25). In our study, AD, MD, RD and FA worths were found to be increased in the capsula interna and capsula externa in the patient than the control group. Most studies showed that an increased FA and RD in capsula externa and capsula interna for HD, PreHD than healthy controls (11,22,2). In this study, AD, MD, RD and FA worths were determined to be increment in the patient group in the fasciculus longitudinalis superior and fasciculus longitudinalis inferior by comparison to the control group. Most studies noticed that a declined FA

and an increment MD, AD, RD in fasciculus longitudinalis superior and fasciculus longitudinalis inferior for HD, PreHD than healthy controls (10,11,22,26,27). Saba et al. stated that decrease in FA is an indicator of a degenerative process and axonal loss (11).

Harrington et al. found that some cognitive areas such as motor planning, verbal learning, memory, sensory-perceptual processing were affected (28). In our study, AD, MD, RD and FA worths were found to be increased in the sagittal stratum and cingulum in the patient group than control group. Most studies indicated that declined FA and increment MD in cingulum for HD, PreHD by comparison to healthy controls (22,26). In this study AD, MD, RD and FA worths were higher in the cingulum patient group than control group. Most studies showed that a declined FA in corona radiata for HD, PreHD by comparison to healthy controls (10,11,22). In our study, AD, MD, RD worths were found to be increased in the corpus callosum parts of the patient group than control group. Rosas et al. found a decrease in FA in the truncus corporis callosi, genu corporis callosi and splenium corporis callosi parts in the patient group by compared to controls (29). Rosas et al. proposed that an increment in RD and AD in fibers of corpus callosum (30). Mazerolle et al. stated that damage in the corpus callosum may affect the transfer of cognitive, sensory and motor knowledge among cortical areas (31). Matsui et al. found that increment FA and RD in the prefrontal white matter tracts in PreHD (24). Liu et al. explained that this showed the corpus callosum also showed demyelination as well as axonal degeneration in preHD (31). Most works indicated that a decline in FA and increment AD, MD, RD and in a corpus callosum regions for HD, PreHD than healthy controls (8-11,16,22,25). Subcortical nuclei had been extensively studied in those with HD. In our study, AD, MD, RD values in subcortical nuclei in the patient group increased than the control group. Most studies showed that an increased FA, MD in subcortical regions for HD, PreHD compared to healthy controls (6,7). In this study we found an increase in MD, RD and AD worths in the nucleus caudatus in the patient than the control group, and there was an increment in the FA worths and it was found to be significant. Rosas et al. indicated that a substantial difference in FA in the nuc caudatus in PreHD and HD patients (29). Novak et al. suggested that white matter microstructural alterations in individuals with HD were related with alterations in the volume of the nucleus caudatus (26). Most studies showed that an increased FA and decreased MD in nucleus caudatus for HD, PreHD than healthy controls (26,32). One study showed that a decline FA and increment MD in nucleus caudatus for HD, PreHD compared to healthy controls (3). In our study, we found an increment in AD, MD, RD, FA and worths in the corpus striatum in the patient group than the control group. Scientists showed that a decline in the FA worth in the corpus striatum and an increment in the MD value in the HD group than the healthy control group were found (9). Despite this, another study indicated that an increase in FA value in the corpus striatum in the HD group than

healthy control group (7). Multiple studies showed that an increased FA in globus pallidus for HD, PreHD than healthy controls (8,28,32). In our study, AD, MD, RD, FA worths were determined increment in the putamen and thalamus in the patient group than control group. Most studies showed an increased FA, MD in putamen, thalamus for HD, PreHD in comparison with healthy controls (7,8,29,32). Odish et al. noticed that the proportion of longitudinal spread alteration in gyrus occipitalis medius, gyrus occipitalis superior, and gyrus occipitalis inferior was substantially higher in the patient group compared to both preHD and controls. They interpreted this as an increasing proportion of microstructural degeneration (33).

In summary, when controls and HD were compared, MD and AD in frontal, parietal, temporal, occipital, corpus callosum, white matter, limbic and subcortical structures, RD in corpus callosum and capsular interna appear to be increased. The FA worths was higher in the nucleus caudatus and putamen and a significant difference was observed. It suggested dysmyelination in these regions. FA worths in the nucleus caudatus and putamen were significant and could be an indicator of a degenerative process, axon loss and inflammation in these regions.

Limitations

The current study had some limitations, (1) the number of HD groups and control groups was small. The reason for this was that HD was a rare genetically inherited neurodegenerative disease and they did not want to have an MRI.

CONCLUSION

We could not find a study in which all regions of the brain were examined in the literature review in studies using the DTI technique in Huntington's disease. Neurodegeneration is connected to the continuous and progressive loss of neurons that occurs in the structure of neurons. Early detection of neurodegeneration is very substantial for the improving of neuroprotective treatments for neurodegenerative illnesses in the future. Studies showed that myelin is an important neuropathological feature of neurodegenerative diseases. In conclusion, using the DTI technique, changes in diffusion parameters can be used as an alternative method to determine biomarkers of disease progression and the microstructural varies in HD. In addition, we believe that conducting studies on more patients to clarify the relationship among DTI measurements and clinical features will yield effective results on the course of the disease.

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REFERENCES

1. MacDonald ME, Ambrose CM, Duyao MP, et al. Huntington Study Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell*. 1993;72:971-83.
2. Ross CA, Aylward EH, Wild EJ, et al. Huntington disease: natural history, biomarkers and prospects for therapeutics. *Nat Rev Neurol*. 2014;10:204-16.
3. Assaf Y, Pasternak O. Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review. *J Mol Neurosci*. 2008;34:51-61.
4. Sprengelmeyer R, Orth M, Muller HP, et al. The neuroanatomy of subthreshold depressive symptoms in Huntington's disease: a combined diffusion tensor imaging (DTI) and voxel-based morphometry (VBM) study. *Psychol Med*. 2014;44:1867-78.
5. Kurtoğlu E, Payas A, Düz S, et al. Analysis of changes in brain morphological structure of taekwondo athletes by diffusion tensor imaging. *J Chem Neuroanat*. 2023;129:102250.
6. Müller HP, Grön G, Sprengelmeyer R, et al. Evaluating multicenter DTI data in Huntington's disease on site specific effects: An ex post facto approach. *Neuroimage Clin*. 2013;32:161-7.
7. Douaud G, Behrens TE, Poupon C, et al. In vivo evidence for the selective subcortical degeneration in Huntington's disease. *NeuroImage*. 2009;46:958-66.
8. Andica C, Kamagata K, Hatano T, et al. MR biomarkers of degenerative brain disorders derived from diffusion imaging. *J Magn Reson Imaging*. 2020;52:1620-36.
9. Muhlau M, Weindl A, Wolschlagel AM, et al. Voxel-based morphometry indicates relative preservation of the limbic prefrontal cortex in early Huntington disease. *J Neural Transm*. 2007;114:367-72.
10. Zhang J, Gregory S, Scahill RI, et al. In vivo characterization of white matter pathology in pre-manifest Huntington's disease. *Ann Neurol*. 2018;84:497-504.
11. Saba RA, Yared JH, Doring TM, et al. Diffusion tensor imaging of brain white matter in Huntington gene mutation individuals. *Arq Neuropsiquiatr*. 2017;75:503-8.
12. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behavior Research Methods*. 2009;41:1149-60.
13. Mori S, Wu D, Ceritoglu C, et al. Mricloud: delivering high-throughput mri neuroinformatics as cloud-based software as a service. *Computing in Science & Engineering*. 2016;18:21-35.
14. Soysal H, Acer N, Özdemir M, et al. A volumetric study of the corpus callosum in the Turkish population. *J Neurol Surg B Skull Base*. 2021;83:443-50.
15. Turamanlar O, Kundakci YE, Saritas A, et al. Automatic segmentation of the cerebellum using volBrain software in normal paediatric population. *Int J Dev Neurosci*. 2023;83:323-32.
16. Ceritoglu C, Tang X, Chow M, et al. Computational analysis of LDDMM for brain mapping. *Front Neurosci*. 2013;7:15.

17. Tang X, Oishi K, Faria AV, et al. Bayesian parameter estimation and segmentation in the multi-atlas random orbit model. *PLoS One*. 2013;8:e65591.
18. Acer N, Kamaşak B, Karapınar B, et al. A comparison of automated segmentation and manual tracing of magnetic resonance imaging to quantify lateral ventricle volumes. *Erciyes Med J*. 2022;44:148-55.
19. Mukherjee P, Berman JI, Chung SW, et al. Diffusion tensor MR imaging and fiber tractography: theoretic underpinnings. *AJNR Am J Neuroradiol*. 2008;29:632-41.
20. Öz F, Acer N, Ceviz Y, et al. Volumetric analysis of the brain structures of children with Down's Syndrome: a 3D MRI study. *J Exp Clin Med*. 2021;38:197-203.
21. Yoshida S, Oishi K, Faria AV, et al. Diffusion tensor imaging of normal brain development. *Pediatr Radiol*. 2013;43:15-27.
22. Sweidan W, Bao F, Bozorgzad NS, et al. White and gray matter abnormalities in manifest Huntington's disease: cross-sectional and longitudinal analysis. *J Neuroimaging*. 2020;30:351-8.
23. Ciarmiello A, Cannella M, Lastoria S, et al. Brain white-matter volume loss and glucose hypometabolism precede the clinical symptoms of Huntington's disease. *J Nucl Med*. 2006;47:215-22.
24. Matsui JT, Vaidya, JG, Johnson HJ, et al. Diffusion weighted imaging of prefrontal cortex in prodromal Huntington's disease. *Hum Brain Mapp*. 2014;35:1562-73.
25. Klöppel S, Draganski B, Golding CV, et al. White matter connections reflect changes in voluntary-guided saccades in pre-symptomatic Huntington's disease. *Brain*. 2008;13:196-204.
26. Novak MJU, Seunarine KK, Gibbard CR, et al. White matter integrity in premanifest and early Huntington's disease is related to caudate loss and disease progression. *Cortex*. 2014;52:98-112.
27. Di Carlo DT, Benedetto N, Duffau H, et al. Microsurgical anatomy of the sagittal stratum. *Acta Neurochirurgica*. 2019;161:2319-27.
28. Harrington DL, Smith MM, Zhang Y, et al. Cognitive domains that predict time to diagnosis in prodromal Huntington disease. *J Neurol Neurosurg Psychiatry*. 2012;83:612-9.
29. Rosas HD, Tuch DS, Hevelone ND, et al. Diffusion tensor imaging in presymptomatic and early Huntington's disease: Selective white matter pathology and its relationship to clinical measures. *Mov Disord*. 2006;21:1317-25.
30. Rosas HD, Lee SY, Bender AC, et al. Altered white matter microstructure in the corpus callosum in Huntington's disease: Implications for cortical "disconnection". *NeuroImage*. 2010;49:2995-3004.
31. Mazerolle E, D'Arcy RC, Beyea SD. Detecting functional magnetic resonance imaging activation in white matter: interhemispheric transfer across the corpus callosum. *BMC Neurosci*. 2008;9:84.
32. Liu W, Yang J, Burgunder J, et al. Diffusion imaging studies of Huntington's disease: a meta-analysis. *Parkinsonism & Related Disorders*, 2016;32:94-101.
33. Odish OFF, Reijntjes RHAM, van den Bogaard SJA, et al. Progressive microstructural changes of the occipital cortex in Huntington's disease. *Brain Imaging and Behavior*, 2018;12:1786-94.



Work-Related Musculoskeletal Pain in Hospital Employees

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Abstract

Aim: Work-related musculoskeletal disorders are common health problems in the community. They lead to various levels of pain, loss of function, and deterioration in quality of life. Our aim is to evaluate work-related musculoskeletal pain in hospital employees and factors that could prevent this problem.

Material and Method: Female and male hospital employees working in different departments of our hospital participated in the study. Demographic data, work and working environment, ergonomic training, and musculoskeletal pain were queried. The severity of pain in those experiencing it was assessed using the visual analog scale and the Nordic Musculoskeletal Questionnaire.

Results: A total of 275 individuals participated in the study. 72.4% of the participants were female and 27.6% were male. 79.3% of the participants reported musculoskeletal pain. Pain was most commonly (71.3%) observed in the 35-54 age group and was of moderate severity. According to the frequency of pain, it was most common in the back (61.5%), followed by the lower back (55.6%) and neck (53.5%) regions. The presence and severity of pain were more pronounced in females ($p<0.05$). There was a statistically significant relationship between the presence of pain and female gender ($p=0.003$, $r=0.179$). Pain severity was higher in females ($p<0.001$, $r=0.226$). 69.8% of healthcare workers reported that ergonomic arrangements were not made in the hospital, and 81.4% reported not receiving training in ergonomics.

Conclusion: Work-related musculoskeletal pain was highly prevalent among hospital healthcare workers, and it was found that healthcare workers did not receive ergonomic arrangements in their work environments or education on protecting the musculoskeletal system. Inference: We believe that making ergonomic adjustments in the work environments of hospital employees, providing education on musculoskeletal system protection, and integrating these into the quality system would be important.

Keywords: Ergonomics, education, musculoskeletal pain

INTRODUCTION

Work-related musculoskeletal disorders are one of the common health issues nowadays. The most frequent cause is inflammatory and degenerative conditions of ligaments, muscles, bones, and joints resulting from repetitive injuries. Pain and loss of function are the most significant symptoms. Musculoskeletal pain leads to limitations and inadequacies in a person's job performance. In Northern Europe, musculoskeletal disorders account for 28% of absenteeism from work. Moreover, they are a cause of high treatment expenses, loss of workforce, insurance compensations, and economic loss (1,2).

The risk factors causing work-related musculoskeletal disorders are divided into three categories: physical-ergonomic, psychosocial, and personal risk factors, which

are interrelated (3). Healthcare system employees perform daily activities that may lead to musculoskeletal disorders. Prolonged work in inappropriate posture, improper use of chairs or desks, heavy lifting, repetitive and vibrational movements, prolonged bending, and strenuous activities are physical and ergonomic risk factors. Psychosocial risk factors include job stress, lack of a production standard, monotony, tension in the work environment, excessive job expectations, inadequate support in job relationships, and lack of support from supervisors. Personal risk factors include being female, age, smoking, overweight, low muscle strength, physical inactivity, and existing musculoskeletal diseases. The intense pace of workload, long and uninterrupted work hours, and tension at work pose a higher risk for healthcare workers compared to other professional groups (3,4).

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Ergonomics is a work method used to understand the complex relationship between humans, machines, and job demands and to minimize the gap between human capacity and job demand in daily life and work activities (5). Recently, research evaluating the impact of ergonomics training provided to hospital employees on musculoskeletal disorders has gained importance (6). Hospital workers are constantly interacting with technology, including fixed and portable tools. This interaction significantly affects human performance. Physical, verbal, and non-verbal communication such as lighting, temperature, noise, radiation, clutter, patient access, and inadequate tool usage, cognitive factors such as workload and stress, decision-making, human-machine interaction, system design, appropriate human placement, employer and employee training, employee supervision, rotational work, regulation of work and rest periods, behavior modification, and use of protective equipment are organizational factors directly affecting system performance in the hospital environment (5,6).

Our aim is to determine the frequency of work-related musculoskeletal pain and factors that may contribute to this problem in order to protect the health of healthcare personnel working in our hospital, increase job satisfaction, and prevent situations that may lead to job loss.

MATERIAL AND METHOD

A descriptive, cross-sectional study was conducted with voluntary female and male individuals aged 18 and above who signed the informed consent form and worked in various departments of İzmir Bakırçay University Faculty of Medicine Çiğli Training and Research Hospital. Ethics committee approval was obtained from İzmir Bakırçay University (Ethics Committee No: 475). The demographic data, work environment characteristics, whether they received ergonomic training to protect the musculoskeletal system, and the presence of musculoskeletal pain were queried. The severity of pain was evaluated using the visual analog scale (VAS) and the Nordic Musculoskeletal Questionnaire (NMQ) (7). The participants' personal characteristics such as age, gender, height, weight, occupation, years and type of employment, presence of chronic diseases, smoking status, and job stress were also examined. Data regarding the characteristics of the work environment such as ventilation, presence of noise, lighting, and relationships with colleagues were collected.

The presence of musculoskeletal pain was questioned. In those experiencing pain, the severity of pain was evaluated using the visual analog scale (VAS). VAS scores were grouped as one to four points=mild, five to six points=moderate, and seven and above points=severe. The Nordic Musculoskeletal Questionnaire (NMQ) was used to assess the pain status and disability. The cultural adaptation study of the NMQ questionnaire was conducted by Kahraman et al. (8). The NMQ questionnaire evaluates complaints of the back, neck, shoulders, and general musculoskeletal system. The individual fills out

the questionnaire by self-reporting or through interview technique, marking specific nine symptom areas mapped on the body (feet-ankles, knees, thighs-hips, wrists-hands, back, elbows, shoulders, neck) (9).

Statistical Analysis

Descriptive statistics were used to present parameters as mean (SD) or n (%). Spearman rank-order correlation test was applied to show factors affecting pain. A p-value of $p < 0.05$ was defined for statistical significance.

RESULTS

A total of 275 hospital employees participated in the study. Of the participants, 199 (72.4%) were female and 76 (27.6%) were male. The most common age range among participants was 35-54 years, accounting for 71.3%. Among the participants, 103 (37.4%) were auxiliary healthcare staff, 84 (30.5%) were nurses, 31 (11.3%) were security guards, 21 (7.6%) were data entry clerks, 20 (7.3%) were doctors, and 16 (5.8%) were cleaning staff. Table 1 shows the demographic data of hospital employees.

Table 1. Demographic data of hospital employees

	n (%)
Gender	
Female	199 (72.4)
Male	76 (27.6)
Age range	
18-24 years	6 (2.2)
25-34 years	68 (24.7)
35-44 years	125 (45.5)
45-54 years	71 (25.8)
55-64 years	5 (1.8)
Marital status	
Married	197 (71.6)
Single	70 (25.4)
Widowed	8 (3.0)
Presence of chronic illness	
Yes	58 (21.1)
No	217 (78.9)
Exercise status	
Regular	42 (15.3)
Irregular	98 (35.6)
No	135 (49.1)
n: number of patients, %: percentage	

When queried about the work and working environment, the average working duration was found to be 14.0 ± 9.1 years. Table 2 presents the characteristics of the work and working environment.

Table 2. Characteristics of job and work environment, risk factors of hospital employees	
	n (%)
Work mode	
Standing for >2 hours	118 (42.9)
Sitting for >2 hours	64 (23.3)
Maintaining the same position for >2 hours	28 (10.2)
Pushing/pulling loads of 5 kg and >5 kg	10 (3.6)
Repetitive movements	55 (20)
Daily working hours	
8 hours	197 (71.6)
16 hours	39 (14.2)
24 hours	37 (13.5)
Perceived difficulty of work	
None	13 (4.7)
Mild	21 (7.6)
Moderate	165 (60)
Severe	76 (27.6)
Presence of stress at work	
Yes	236 (85.8)
No	39 (14.2)
Ventilation in the workplace	
Centralized	139 (50.5)
Window	13 (4.7)
Centralized+window	123 (44.7)
Presence of noise in the workplace	
Yes	245 (89.1)
No	30 (11.9)
Lighting in the workplace	
Positive	234 (85.1)
Negative	41 (14.9)
Work relationships in the workplace	
Positive	245 (89.1)
Negative	30 (10.9)
Ergonomic arrangements in the workplace	
Yes	83 (30.2)
No	192 (69.8)
Training for musculoskeletal system protection in the workplace	
Yes	52 (18.9)
No	223 (81.4)

n: number of patients, %: percentage

In the query regarding musculoskeletal pain, it was reported that 218 cases (79.3%) experienced pain. Among those with pain, the severity was as follows: 90

cases (41.2%) reported moderate pain, 72 cases (33.1%) reported mild pain, and 56 cases (25.6%) reported severe pain. There was a statistically significant relationship between the presence of pain and female gender ($p=0.003$, $r=0.179$). Pain severity was statistically higher in females ($p<0.001$, $r=0.226$). As the duration of work increased, both the occurrence and severity of pain increased ($p=0.009$, $p=0.008$). When painful areas were evaluated with the NMQ (Nordic Musculoskeletal Questionnaire) in Table 3, spinal pain in the last twelve months was reported in the following order of frequency: back, lower back, and neck. In the extremities, shoulder pain was most common in the upper extremity, while knee pain was predominant in the lower extremity.

Table 3. The nordic musculoskeletal questionnaire (NMQ)

	Pain in the last 12 months		Work limitation due to pain in the last 12 months		Pain in the last 7 days	
	Yes n (%)	No n (%)	Yes n (%)	No n (%)	Yes n (%)	No n (%)
Neck	147 (53.5)	128 (46.5)	82 (29.8)	193 (70.2)	87 (31.6)	188 (68.4)
Shoulder	134 (48.7)	141 (51.3)	60 (21.8)	215 (78.2)	101 (36.7)	174 (63.3)
Elbows	46 (16.7)	229 (83.3)	29 (10.5)	246 (89.5)	64 (23.3)	211 (76.7)
Hand	88 (32)	187 (68)	47 (17.1)	228 (82.9)	59 (21.5)	216 (78.5)
Sirt	169 (61.5)	106 (38.5)	82 (29.8)	193 (70.2)	118 (42.9)	157 (57.1)
Back	153 (55.6)	122 (44.4)	85 (30.9)	190 (69.1)	113 (41.1)	162 (58.9)
Hip/thig	75 (27.3)	200 (72.7)	46 (16.7)	229 (83.3)	58 (21.1)	217 (78.9)
Knee	105 (38.2)	170 (61.8)	47 (17.1)	228 (82.9)	66 (24)	209 (76)
Ankle/foot	89 (32.4)	186 (67.6)	42 (15.3)	233 (84.7)	59 (21.5)	126 (45.5)

n: number of patients, %: percentage

DISCUSSION

In our study, we found a high incidence of musculoskeletal pain among hospital employees. Hou et al. reported musculoskeletal disorders in nurses at 92%, while Smith et al. reported it at 86% in our country. In studies conducted by Sançar et al., this rate reached up to 48% (10-13). A study investigating musculoskeletal disorders related to working conditions and profession in physicians reported a problem in 33% of 123 physicians, most commonly seen in surgeons. The prevalence of musculoskeletal disorders in nurses varies between 35-80% (14).

Healthcare workers engage in daily activities that lead to musculoskeletal pain. Inappropriate postural positions, ergonomic deficiencies, and heavy work conditions during

hospital work lead to occupational problems. Bret et al. reported that prolonged work in the same position and inappropriate posture are significant factors, which is consistent with our study, especially emphasizing their occurrence in the back and lower back regions (3). The prevalence of back pain was high, reaching around 70% in surgeons and dentists. The frequency of lower back pain was above 50% in surgeons, physiotherapists, and nurses. Davis et al. reported that the highest prevalence of pain in nurses and nursing assistants was in the lower back, followed by the shoulder and neck regions. This prevalence was even higher in the home care group, which deals with patients with chronic diseases who live for long periods with reduced mobility (15).

Maintaining a certain posture for a long time during work depends on stabilizing and manipulative forces, leading to prolonged isometric muscle contractions and increasing stress on muscles and ligaments. This, in turn, leads to muscle fatigue. Studies show that early degenerative changes in the lumbar region are due to compression, bending, and shearing stresses resulting from incorrect movements (16). Standing for a long time and working in a bent position increases the load on the spine and affects posture. Posture is directly related to mechanical efficiency and physiological function. Regular exercise strengthens muscles, provides soft tissue flexibility, and ensures mechanical efficiency. The fact that only 15% of participants in our study engaged in regular exercise may pose a risk factor for pain.

In our study, 85.8% of the participants reported experiencing stress in the workplace. The healthcare sector is considered an environment with higher levels of work-related stress compared to other work environments, both due to serving individuals experiencing high levels of stress and the frequent encounters of the staff with stressful situations. Dilek and colleagues reported a close relationship between musculoskeletal pain and stress levels (17). Hamming et al. evaluated musculoskeletal and sleep disorders related to work and stress in healthcare professionals, finding a high association between musculoskeletal pain, stress, and sleep disorders, emphasizing that work stress, especially when combined with physical workload, significantly increases pain (18). Yona et al. highlighted the necessity of assessing individuals for depressive symptoms accompanying musculoskeletal pain among hospital employees (19). According to the literature, being female is considered a risk factor for pain, with women having a lower pain threshold and experiencing musculoskeletal pain twice as often as men. The high number of female participants in our study may also contribute to this finding (20). Additionally, Shirzai et al. found that in their study evaluating upper extremity pain among hospital employees, pain severity was higher in women (21).

It is reported that providing ergonomics training focused on body biomechanics to nurses increases work capacity. When there is a mismatch between the physical requirements of the job and the worker's physical capacity,

the incidence of work-related illnesses increases (22). Attention to posture and prevention principles, along with ergonomic factors, plays a significant role in the development of occupational pain and illnesses among healthcare workers. Implementing ergonomic principles in hospitals can help reduce repetitive movements and physical strain. Additionally, teaching regular exercise and pain management techniques to employees is beneficial. Furthermore, providing regular breaks during work contributes to productivity and positive effects on work performance by allowing muscles to rest and reducing fatigue. To improve the quality of life of employees working in hospital environments, an ergonomic patient care system should be established that is compatible with physical, social, and psychological characteristics.

For this purpose, we believe that making ergonomic adjustments in work environments, providing musculoskeletal protection training, and integrating these into the quality system would be important.

Limitations of the study include the small number of participants and the disproportionate distribution of occupational groups.

CONCLUSION

In our study, there was a high incidence of musculoskeletal pain among hospital employees. Pain was most commonly reported in the back, lower back, and neck. The presence and severity of pain were particularly pronounced in females. Prolonged inappropriate posture and repetitive movements were significant contributing factors.

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REFERENCES

1. Madeleine P, Vangsgaard S, Hviid Andersen J, et al. Computer work and self-reported variables on anthropometrics, computer usage, work ability, productivity, pain, and physical activity. *BMC Musculoskelet Disord.* 2013;14:226.
2. Luger T, Maher C, Rieger MA, Steinhilber B. Work break schedules for preventing musculoskeletal symptoms and disorders in healthy workers. *Cochrane Database Syst Rev.* 2019;7:CD012886.
3. Chen H, Huang PY, Chuang HY, et al. Association of low back pain with shift work: a meta-analysis. *Int J Environ Res Public Health.* 2023;20:918.
4. Özcan E, Esmaeilzadeh S, Başat H. Upper extremity work-related musculoskeletal disorders among computer users and effectiveness of ergonomic interventions. *Turk J Phys Med Rehab.* 2011;57:236-41.
5. Kim H, Dropkin J, Spaeth K, et al. Patient handling and

- musculoskeletal disorders among hospital workers: analysis of 7 years of institutional workers' compensation claims data. *Am J Ind Med.* 2012;55:683-90.
6. Abdollahi T, Razi S, Pahlevan D et al. Effect of an ergonomics educational program on musculoskeletal disorders in nursing staff working in the operating room: a quasi-randomized controlled clinical trial. *Int J Environ Res Public Health.* 2020;17:7333.
 7. Kuorinka I, Jonsson B, Kilbom A, et al. Standardised Nordic questionnaires for the analysis of musculoskeletal symptoms. *Appl Ergon.* 1987;18:233-7.
 8. Kahraman T, Genç A, Göz E. The Nordic Musculoskeletal Questionnaire: cross cultural adaptation into Turkish assessing its psychometric properties. *Disabil Rehabil.* 2016;38:2153-60.
 9. Kandemir D, Karaman A, Uğraş G, Öztekin SD. Examination of musculoskeletal pain operating room nurses. *J Educ Res Nurs.* 2019;16:1-7.
 10. Dıraçoğlu D. Musculoskeletal pain among medical staff. *Türkiye Klinikleri J Med Sci.* 2006;26:132-9.
 11. Sancar B, Taş S, Aktaş D. Determining prevalence of work-related musculoskeletal disorders and related factors in nurses. *Huhemfad-Johufon.* 2021;8:231-8.
 12. Hou JY, Shiao JSC. Risk factors for musculoskeletal discomfort in nurses. *J Nurs Res.* 2006;14:228-36.
 13. Smith DR, Mihashi M, Adachi Y, et al. A detailed analysis of musculoskeletal disorder risk factors among Japanese nurses. *J Safety Res.* 2006;37:195-200.
 14. Babayigit MA, Kurt M. Hospital ergonomics. *İstnbul Med J.* 2013;14:153-9.
 15. Davis K, Kotowsky S. Prevalence of musculoskeletal disorders for nurses in hospitals, long term care facilities and home healthy care: a comprehensive review. *Hum Factors.* 2015;57:794-2.
 16. Herman H. Postural and motor strain at video display terminal. *Advances in Applied Ergonomics: Proceedings of the 1st International Conference on Applied Ergonomics (Icae'96), 21-24 May 1996, İstanbul, Türkiye, 221-2.*
 17. Dilek B, Korkmaz F, Baş G, et al. Evaluation of musculoskeletal problems and quality of life in physicians who work in a university hospital. *DEU Tıp Derg.* 2016;30:25-30.
 18. Hämmig O. Work- and stress-related musculoskeletal and sleep disorders among health professionals: a cross-sectional study in a hospital setting in Switzerland. *BMC Musculoskelet Disord.* 2020;21:319.
 19. Yona T, Weisman A, Gottlieb U, Masharawi Y. High levels of self-reported depressive symptoms among physical therapists and physical therapist students are associated with musculoskeletal pain: a cross-sectional study. *Phys Ther.* 2022;102:pzab278.
 20. Burri A, Lachance G, Williams FM. Prevalence and risk factors of sexual problems and sexual distress in a sample of women suffering from chronic widespread pain. *J Sex Med.* 2014;11:2772-84.
 21. Şirzai H, Doğu B, Erdem P, et al. Work-related musculoskeletal diseases in hospital workers: upper extremity problems. *Ş.E.E.A.H. Tıp Bülteni.* 2015;49:135-41.
 22. Hartvigsen J, Lauritzen S, Lings S, Lauritzen T. Intensive education combined with low tech ergonomic intervention does not prevent low back pain in nurses. *Occup Environ Med.* 2005;62:13-7.