e-ISSN: 2636-8579

JHSM

Journal of Health Sciences and Medicine

VOLUME: 7 ISSUE: 3 YEAR: 2024

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HEALTH SCIENCES
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DOI: 10.32322/jhsm.1451075
J Health Sci Med. 2024;7(3):247-251

Clinical significance of pretreatment De Ritis ratio in renal cell carcinoma

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Cite this article as: Kölükçü E, Fırat F, Yalçın K, Balcı ŞY, Kuyucu YE. Clinical significance of pretreatment De Ritis ratio in renal cell carcinoma. *J Health Sci Med.* 2024;7(3):247-251.

Received: 11.03.2024 ◆ **Accepted**: 01.04.2024 ◆ **Published**: 27.05.2024

ABSTRACT

Aims: This study aimed to investigate the relationship between pretreatment De Ritis ratio and Fuhrman nuclear grade and tumor stage in renal cell carcinoma (RCC).

Methods: The data of 288 patients treated for RCC were analyzed. The De Ritis ratio was evaluated in patients classified by Fuhrman nuclear grade and tumor stage. The De Ritis ratio between groups was compared using Levene's test.

Results: A total of 145 patients (50.3%) were women female. Their mean age, aspartate aminotransferase, alanine aminotransferase values, and De Ritis ratio were as follows, respectively: 60.32±12.65 years, 20.55±11.54 IU/L, 17.4±10.87 IU/L, and 1.34±0.75. The De Ritis ratio was 1.12±0.44 in the low stage group and 2.01±1.05 in the high stage group. According to the Fuhrman nuclear grading, the De Ritis ratio was 1.15±0.43 in the low grade group and 1.70±1.14 in the high grade group. There was a statistically significant difference between the groups ($p<0.001$).

Conclusion: The present study showed high preoperative De Ritis ratio is significantly correlated with high tumor stage and Fuhrman nuclear grade in RCC.

Keywords: De Ritis ratio, transaminases, renal cell carcinoma, furhman grade

INTRODUCTION

Renal tumors constitute approximately 3% of all malignancies seen in adulthood. It is the third most common urogenital malignancy following prostate and bladder cancers. According to histopathological analyses, 80-85% of all renal tumors were composed of renal cell carcinomas (RCC).[1] RCCs are more frequently observed in industrial societies and many factors such as obesity, hypertension, and smoking are blamed in the etiology. It is 1.5 times more common in males than in females, with a significant increase in the incidence of diagnosis in the 6th and 7th decades of life. Clinical presentation of RCC patients shows variation.[2] Only 6-10% of diagnosed cases present with the classic triad of RCC: gross hematuria, side pain, and a palpable abdominal mass.[3] Surgical resection is the only curative treatment option. 1/3 of the patients are metastatic at the time of diagnosis and another 1/3 may develop metastasis after treatment.[4]

In parallel with the developments in the field of uroradiology and the increased awareness of the patients, the number of RCC cases diagnosed has increased significantly over the years. Current literature suggests that RCC incidence has increased by 2-4% worldwide over the last decade.[5] The increased knowledge of RCC cases has led to different approaches regarding the clinical impression of the disease. In this context, promising improvements in prognosis have been observed. For example, the timing of cytoreductive nephrectomy in RCC has been recognized and proved to be indisputable. In addition, pharmacological agents, such as immunotherapy and targeted therapy, have entered clinical practice.[6] However, despite all these developments, RCC remains the most mortal urologic malignancy.[1] Therefore, the molecular biological character of RCC is important in developing an optimal treatment strategy against recurrent diseases and determining follow-up protocols. For this reason, it is very important to investigate prognostic markers in RCC patients.[7]

Alanine aminotransaminase (ALT) and aspartate aminotransaminase (AST) are liver enzymes commonly used in clinical laboratory tests.[8] The De Ritis ratio, calculated by dividing AST by ALT, was first described by Fernando De Ritis in 1957 as a diagnostic marker for viral hepatitis.[8,9] It is also used as an independent predictor of patient survival in chronic liver diseases.[10] On the other hand, intensive research has been carried out recently to show that the ratio of De Ritis will change in various malignancies according to the differences in the functions of these two enzymes in tissue distribution and energy metabolism.[7] In this context, previous clinical studies have reported that De Ritis ratio may be prognostic factors in urological tumors such as kidney, prostate, and bladder.[11-13]

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This retrospective study aimed to investigate the relationship of the preoperative De Ritis ratio with Fuhrman nuclear grade and tumor stage in patients who underwent partial or radical nephrectomy and were diagnosed with RCC based on histopathological examination

METHODS

Medical record of patients who underwent partial or radical nephrectomy in our clinic between January 2011 and May 2023 were analyzed retrospectively. A total of 288 patients patients, who received the diagnosis of RCC based on histopathological investigation were included. The Tokat Gaziosmanpaşa University Faculty of Medicine Clinical Researches Ethics Committee (Date: 13.07.2023, Decision No: 23-KAEK-162) approved this study. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The patients' ages, genders, ALT and AST levels were noted preoperatively. Pathological T stage, histological subtypes, Fuhrman nuclear grade of tissue samples were analyzed.[1,14-16] Surgical specimens were assessed for tumor grades and stage using the Fuhrman system and 2018 TNM classification respectively.[14] The De Ritis ratio, calculated by dividing AST by ALT.[8]

According to Fuhrman nuclear grade, Grade 1 and 2 patients were defined as low grade and the others as high grade. Similarly, stage 1 and stage 2 patients were classified as low stage and others as high stage. Fuhrman grade is not used in chromophobe RCC, renal medullary carcinoma and unclassified type of RCC due to the aggressive nature of these subgroups.

We excluded patients with a history of hepatitis, chronic liver disease alcoholism, heart failure, drug use that may impair liver enzymes, and any other cancer that may affect the AST/ALT ratio.

Statistical Analysis

Descriptive statistical work-up was conducted fort he study in order to give insight on general characteristics. Data on continuous variables were given as arithmetic mean and standart devision. As for inter-group comparisons of variables indicated with messurements, a t-test was used for independent samples to study inter-group differences. ROC (receiver operating characteristics) curve analysis was applied to determine the cut-off values of the variables, and the area under the Roc curve (AUC) was also evaluated. Levene's test was used to check whether data pertaining to continuous variables matched with normal distribution or not. A p-value of less than 0.05 was considered statistically significant. Calculations were made with available statistical software (IBM SPSS 22, SPSS Inc., an IBM Co., Somers, NY).

RESULTS

A total of 288 patients included in the study, 145 patients (50.3%) were female. The mean age was 60.32±12.65. Ninety nine patients (34.3%) underwent partial nephrectomy, and 189 patients (65.7%) underwent radical nephrectomy. A total of 151 patients (52.43%) were operated on the left side and 137 patients (47.57%) 62 patients (50.4%) on the right side. Seventy one patients (24.65%) had high-grade tumors (T3 or T4), and 217 (75.35%) had low-grade tumors (T1 or T2). In the Fuhrman nuclear grading, 218 patients (82.6%) had low-grade tumors, and 46 patients (17.4%) had high-grade tumors. Surgical specimens were evaluated according to histological subtypes: RCC in 216 patients (75%), papillary in 48 (16.67%), chromophobe in fourteen (4.86%), renal medullary carcinoma in six (2.08%), and an unclassified type of RCC in four (1.39%).

In the classification according to tumor stage, the AST/ALT ratio was 1.12±0.44 and 2.01±1.05 in the low and high-stage groups, respectively (Table). The relationship between low and high tumors was evaluated by ROC analysis. The NLR cut-off value was 0.873, with significant difference between the two groups (p<0.001) (Figure 1). The AST/ALT ratio for low- and high-grade tumors was 1.15±0.43 and 1.70±1.14, respectively. According to the ROC analysis of both groups, the cut-off value was 0.848, which was statistically significant (p<0.001) (Figure 2).

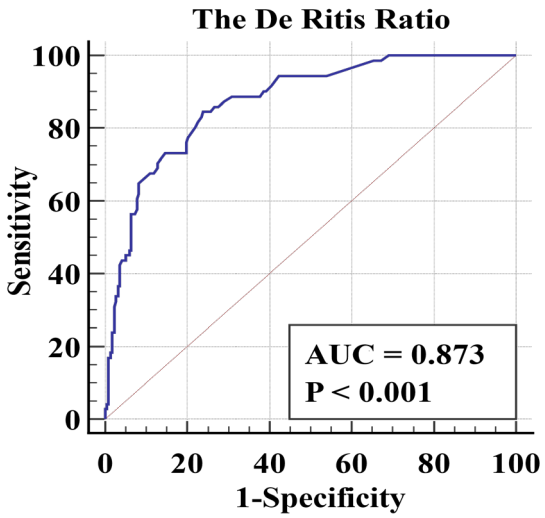

Figure 1. The result of ROC analysis for tumor stage
Area under the Roc curve:0.873, %95 confidence interval:0.829-0.909, significance level p<0.001*, associated criterion:1.25

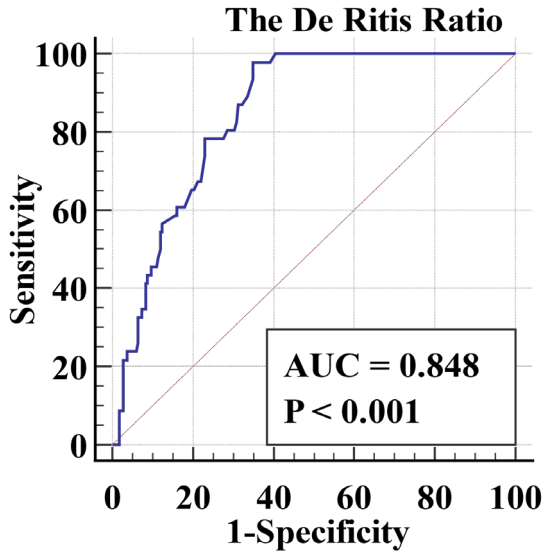

Figure 2. The result of ROC analysis for Fuhrman nuclear grade
Area under the Roc curve:0.848, %95 confidence interval: 0.799-0.889, significance level p<0.001*, associated criterion: 1.17

Table. De Ritis Ratio ratio according to tumor parameters

		n	Mean±SD	p
Tumor stage	Low stage (T1+2)	217	1.12±0.44	<0.001*
	High stage (T3+4)	71	2.01±1.05	
Nuclear grade	Low grade (grade 1+2)	218	1.15±0.43	<0.001*
	High grade (grade 3+4)	46	1.70±1.14	

Indepence samples T test, *: p value is significant less than 0.05

DISCUSSION

RCC is a highly complex disease in terms of histological subgroups, clinical course, and response to treatment. The prognosis is poor in patients diagnosed at the metastatic stage or who develop recurrence after receiving treatment for the local disease. The expected survival in patients presenting with metastasis varies between 6-10 months, with a 2-year survival rate of 10-20%. Local recurrence after radical nephrectomy is rare and ranges from 0.8% to 4% in various series.[17] A better understanding of the molecular biology of RCC, angiogenesis, and related signaling pathways has broadened horizons in the treatment strategies of the disease in recent years. Although there have been significant improvements in the use of targeted agents recently, there is ongoing scientific research on the use of these agents for adjuvant and neoadjuvant purposes. These improvements make it very important to predict the prognosis and response to the treatment chosen for RCC patients. However, clinicians are faced with great difficulties in predicting prognosis as the natural course of RCC is complex and varies from patient to patient.[18,19] TNM staging adapted for all solid tumors is the most important prognostic marker for RCC. In fact, many different prognostic markers have been analyzed in previous studies in the literature.[1] Anatomic prognostic factors include tumor size, venous invasion, capsule invasion, microvascular invasion, lymphovascular invasion, renal sinus fat invasion, perinefric fat invasion, adrenal involvement, lymph node, and distant metastasis. Histologic subgroup, sarcomatoid/rhabdoid transformation, nuclear grade, tumor necrosis, microvascular invasion, and collecting system invasion are evaluated for histopathological prognostic parameters. As for clinical factors, the patient's performance status, the presence of localized symptoms, cachexia, anemia, and thrombocytosis are analyzed.[18,20] In addition, a number of molecular markers have recently been shown to be important prognostic factors. The most prominent ones are carbonic anhydrase 9, hypoxia-inducing factor-1 alpha (HIF-1 alpha), VHL tumor suppressor protein, vascular endothelial growth factor (VEGF), apoptosis regulators (Bcl-2, p53), cell cycle regulators (p27 and Phosphatase-tensin homolog (PTEN), cell adhesion molecules (CD44, EpCam, Eph A2), C-reaktive Protein (CRP), and osteopontin.[18,21] However, due to the lack of standardization as well as the time-consuming and expensive nature of the as says none has been suitable for clinical practice.[11] In this context, the medical disciplines has long been in a search for using biochemical parameters for prediction of postoperative period. De Ritis ratio is one of them.

The relationship between the De Ritis ratio and cancer is based on different hypotheses.[22] Rapidly proliferating tumors convert glucose into lactate in an aerobic environment, although the amount of adenosine triphosphate obtained from one glucose molecule is very small. This feature of cancer cells is called the Warburg effect. Decreasing Ph affects the tumor microenvironment, influencing cancer progression, metastasis, and local invasion.[13] However, lactate elevation plays an essential role in the continuation of glycolysis, and cytosolic nicotinamide adenine dinucleotide hydride/nicotinamide adenine dinucleotide (NADH/NAD) is critical in glucose transport. AST is one of the important components of the malate-aspartate shuttle pathway that allows NADH/NAD conversion.[9,13] In addition, AST is generally produced in different tissue types such as kidney, heart, gastric mucosa, adipose tissue, skeletal muscle, and brain, while ALT is considered more liver-specific. Accordingly, a more serious increase in AST level is observed in tissue damage secondary to oxidative stress.[8,9,12]

The relationship between kidney cancer and De Ritis rate has been studied in detail in recent years. The case series of 698 cases by Bezan et al.[11] reported that the AST/ALT ratio was evaluated preoperatively as an independent prognostic factor in patients with non-metastatic RCC. In another study examining patients with non-metastatic RCC, Canat et al.[7] reported that an increased preoperative AST/ALT ratio was significantly associated with renal pelvis involvement, renal capsule infiltration and renal vein invasion. Ishihara et al.[10] stated that the preoperative AST/ALT ratio is an indicator for cancer-specific survival and overall survival in patients with metastatic RCC who underwent radical nephrectomy. Similarly, Laukhtina et al.[23] observed that a high preoperative De Ritis ratio was closely associated with liver metastasis in their studies evaluating metastatic RCC patients treated with cytoreductive nephrectomy. Lee et al.'s[24] large-series studies including 2965 cases reported that RCC patients with high AST/ALT ratios had significantly worse overall and cancer-specific survival outcomes. A retrospective study by Ikeda et al.[25] observed that the AST/ALT ratio was significantly associated with cancer-specific survival after radical nephrectomy in patients with RCC associated with end-stage renal disease. Kang et al.[26] reported that a high De Ritis ratio is correlated with adverse survival outcomes after first-line tyrosine kinase inhibitor therapy in patients with metastatic RCC. Our study observed that preoperatively increased AST/ALT ratio in patients with RCC was associated with higher postoperative tumor stage and Fuhrman grade. In another study, Batur et al.[27] could not find a significant value for the De Ritis ratio as a predictive parameter in non-metastatic clear cell RCC prognosis. In a similar study, Janisch et al.[28] examined 220 metastatic RCC patients treated with tyrosine kinase inhibitors and could not detect an independent association between the De Ritis rate and survival.

Limitations

The main limitation of our study is that it was conducted retrospectively, with a single center and a limited number of cases.

CONCLUSION

According to the data obtained in our study, preoperatively increased De Ritis ratio is closely associated with high tumor stage and Fuhrman grade. We think multicenter, randomized, and controlled studies are needed to use these data in clinical practice.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Tokat Gaziosmanpaşa University Faculty of Medicine Clinical Researches Ethics Committee (Date: 13.07.2023, Decision No: 23-KAEK-162).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1449241
J Health Sci Med. 2024;7(3):252-258

Cone beam computed tomography evaluation of bone height and width in 7 different tooth regions of totally edentulous maxilla

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Cite this article as: Öner Talmaç AG, Orhan ZD, Ciğerim L, et al. Cone beam computed tomography evaluation of bone height and width in 7 different tooth regions of totally edentulous maxilla. *J Health Sci Med.* 2024;7(3):252-258.

Received: 09.03.2024 ◆ **Accepted**: 02.04.2024 ◆ **Published**: 27.05.2024

ABSTRACT

Aims: The aim of this study was to evaluate the residual alveolar bone height and bone width at different depths from the central tooth region to the second molar tooth region in maxillary totally edentulous individuals.

Methods: This retrospective observational radiographic study was performed on cone beam computed tomography images of patients who presented to the department of oral and maxillofacial surgery for dental implant evaluation between January 2010 and March 2023. Horizontal measurements were taken on sagittal cross-sectional images at vertical depths of 1 mm, 3 mm, 5 mm and 7 mm from the alveolar crest. Vertical measurements were made by measuring the distance between the crest of the alveolar ridge and the base of the nose or the base of the maxillary sinus. The results were evaluated with 95% confidence interval and significance at $p<0.05$ level.

Results: Of the 104 patients included in the study, 42 were male and 62 were female and their age ranged from 36 to 90 years with a mean age of 50.88±10.28 years. The mean change of 0.46±1.83 units in the vertical measurements on the left side compared to the right side in the lateral region was statistically significant ($p<0.05$). Bone height was greater in the right and left central regions than in the 2nd premolar, 1st molar and 2nd molar regions ($p<0.05$). Bone width was greater in the 2nd premolar, 1st molar and 2nd molar regions and on the left side at depths of 1, 3 and 5 mm ($p<0.05$).

Conclusion: This study was the first to compare residual bone height and width at 1, 3, 5 and 7 mm depth from the central region to the second molar region in individuals with complete maxillary edentulism. The study showed that the loss of horizontal bone width as a result of alveolar crest resorption in edentulous patients was advanced and the need for horizontal augmentation was very high in this group of patients being considered for dental implant surgery.

Keywords: Dental implant, maxilla, edentulous maxilla, bone width, bone height

INTRODUCTION

The close relationship between the tooth and the alveolar crest continues throughout life. According to Wolff's law, the bone is remodeled in response to the applied forces. During function, changes occur in the internal and external structure of the alveolar bone. Alveolar crest resorption (ACR) is a chronic, progressive and irreversible process. ACR begins after tooth extraction and is associated with factors such as gender, hormones, metabolism, parafunction and inappropriate dentures. The duration of edentulism is one of the most important factors in ACR.[1-4]

It has been shown that 6 months after tooth extraction, bone width loss is between 29-63% and bone height loss is between 11-22%, and the resorption rate is highest in the first 6 months.[5] After tooth loss, atrophic edentulous ridges can form due to remodelling of the adjacent alveolar bone.[5,6]

As the alveolar crest volume has a direct effect on retention, stability and support of the prosthesis, it plays an important role in success of the prosthesis.[7] ACR is the major cause of stability and retention problems in removable dentures.[8]

Today, implant supported dentures are the first choice in the rehabilitation of edentulous jaws.[3] In individuals with complete edentulism, the effects of ACR increase with the duration of edentulism and rehabilitation of this patient group can be complicated. The width and height of the residual bone are critical in implant-supported prosthetic planning.[9] In cases of complete edentulism, bone width and height should be assessed prior to implant surgery. These assessments should identify areas of adequate and inadequate bone, and planning should be made accordingly.[5] The routine use of cone beam computed tomography (CBCT) is recommended to assess

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the width and height of edentulous ridges.[10] CBCT provides a three-dimensional assessment of the alveolar bone. Implant surgery planned without CBCT is likely to be problematic. Three-dimensional evaluation of the bone allows detection of cases with inadequate bone width and height, allowing modification of the planned implant site(s) or planned bone augmentation in the relevant areas. Preoperative knowledge of the available residual alveolar bone width and height prevents the clinician from encountering an unexpected situation during implant surgery and possible patient compromise.[11,12]

It is clear that radiological accuracy in implant planning is only possible with CBCT. However, despite its widespread use today, the use of CBCT is still limited.[13,14] Therefore, it is important to determine the bone height and width at different depths from the crestal level in different tooth regions for implant planning in the rehabilitation of edentulous patients. There are no studies in the literature that have evaluated edentulous jaws in this regard. In edentulous jaws, it is not known in which tooth(s) the bone width and height are sufficient and insufficient, and the determination of these regions will contribute to implant planning. The aim of this study was to evaluate the residual alveolar bone height and bone width at different depths from the central tooth region to the second molar tooth region in maxillary totally edentulous individuals.

METHODS

This retrospective observational radiographic study was performed on CBCT images of patients who presented to Van Yüzüncü Yıl University Faculty of Dentistry, Department of Oral and Maxillofacial Surgery for dental implant evaluation between January 2010 and March 2023. The study was approved by the Non-interventional Ethics Committee of Van Yüzüncü Yıl University (Date: 17.03.2023, Decision No: 2023/03-09). All procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and the Helsinki Declaration of 1975, as revised in 2008.

Individuals aged 18 years and older, individuals with ASA1 and ASA2 systemic status, individuals who had been totally edentulous for at least 1 year, and individuals with CBCT images of sufficient resolution and showing the entire maxilla were included in the study. Individuals with cleft lip and palate, a history of nasal or maxillary sinus disease, a history of maxillary surgery, jaw pathology or fracture, image artefacts, and poor-quality images were excluded. The CBCT images used in this study were acquired with a Kavo 3D exam (KaVo Dental, Biberach, Germany) tomography unit (image characteristics as follows 0.2-0.4 mm voxel size, 18.54 mAs, 120 kVp, 8.9 seconds scan time and 160×60-130 field of view). CBCT images were analysed using examvision software (KaVo Dental, Biberach, Germany).

All measurements and assessments were performed by an oral and maxillofacial radiologist with 6 years of experience in CBCT image interpretation. Measurements were repeated by the same examiner at two different times, 3 weeks apart, and intraobserver agreement was calculated as 0.95. In the axial section, central points representing the position of each tooth were determined based on the average mesio-distal widths of the right and left maxillary central, lateral, canine, premolar and molar teeth. Crown widths were considered to be 8.87 mm for central, 6.96 mm for lateral, 7.77 mm for canine, 7.08 mm for first premolar, 6.77 mm for second premolar, 10.31 mm for first molar and 9.76 mm for second molar.[15,16] Using the CBCT midline as a reference, the points where the central teeth should be located on the right and left were first determined. The position of each tooth was then determined by calculating the distance from the midline and the midpoint of the previous tooth. Horizontal measurements (bone width measurements) were taken on sagittal cross-sectional images at vertical depths of 1 mm, 3 mm, 5 mm and 7 mm from the alveolar crest. Right and left central (R1), lateral (R2), canine (R3), 1st premolar (R4), 2nd premolar (R5), 1st molar (R6) and 2nd molar (R7) teeth were measured using the same protocol. A total of 56 bone width measurements were taken from 14 points. Width measurements corresponding to the nasal and maxillary sinuses were accepted as "0". Vertical (bone height) measurements were also taken for each tooth from the points where the horizontal measurements were taken. Vertical measurements were made by measuring the distance between the crest of the alveolar ridge (where horizontal measurements were taken at a depth of 1 mm) and the base of the nose or the base of the maxillary sinus (Figure). Power analysis was performed using G*Power (v3.1.9.2) to determine sample size. Based on the study by Katsoulis et al.,[17] the differences between the groups were examined and as a result of the calculation, the effect size was calculated as d=1.0338 and it was calculated that a total of at least 42 patients should be studied to achieve 99% power at α=0.01 level. Between March 2023 and January 2024, when the study was conducted, 104 patients were found to meet the inclusion criteria and all 104 patients were included in the study.

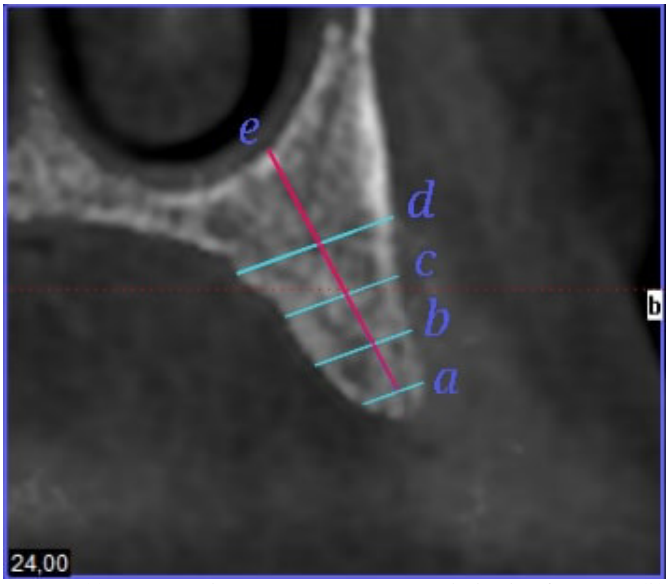

Figure. (a) Horizontal measurement at vertical depth of 1 mm; (b) Horizontal measurement at vertical depth of 3 mm; (c) Horizontal measurement at vertical depth of 5 mm; (d) Horizontal measurement at vertical depth of 7 mm; (e) Vertical measurement which is the distance between the crest of the alveolar ridge (where horizontal measurements were made at a depth of 1 mm) and the base of the nose or the base of the maxillary sinus

Statistical Analysis

NCSS 2020 (Kaysville, Utah, USA) was used for statistical analysis. When evaluating the study data, quantitative variables were presented using mean, standard deviation, median, Q1 and Q3 values, and qualitative variables were presented using descriptive statistical methods such as frequencies and percentages. The Shapiro-Wilks test and box plots were used to assess the suitability of the data for normal distribution. Student's t-test was used to assess two quantitative groups with normal distribution, and paired sample t-test was used for within-group assessments. Pearson correlation analysis was used to assess relationships between variables according to distribution. The results were evaluated with 95% confidence interval and significance at p<0.05 level.

RESULTS

Of the 104 patients included in the study, 40.4% (n=42) were male and 59.6% (n=62) were female and their age ranged from 36 to 90 years with a mean age of 50.88±10.28 years (Table 1).

Table 1. Distribution of descriptive characteristics

		n (%)
Gender	Male	42 (40.4)
	Female	62 (59.6)
Age	*Mean±SD*	50.88±10.28
	Median (min-max)	59 (36-90)

SD: Standart deviation, Min: Minimum, Max: Maximum

Evaluation of Vertical Measurements

There was a statistically significant difference in the mean vertical measurements on the left side compared to the right side in the lateral region (p=0.011; p<0.05). In other regions, the changes in the vertical measurements on the left side compared to the right side were not statistically significant (p>0.05) (Table 2).

Table 2. Comparison of vertical measurements in the regions by side

	Right maxilla		Left maxilla			
Vertical	Mean±SD	Median(IQR)	Mean±SD	Median(IQR)	Change	[a]p
R1	15.15±3.58	15.3 (12.7-17.6)	15.64±3.82	16.1 (13.7-18.2)	-0.48±2.67	0.065
R2	14.42±3.44	14.7 (12.5-16.6)	14.89±3.55	15.5 (12.6-17.1)	-0.46±1.83	0.011*
R3	14.57±3.60	14.4 (12.5-17)	14.46±3.61	14.5 (12.1-16.6)	0.10±2.19	0.626
R4	13.41±4.52	13.7 (10.5-16.2)	13.73±4.23	14 (10.6-16.7)	-0.31±3.75	0.393
R5	10.39±5.10	10 (7.2-13.6)	10.83±5.02	11 (7.4-14.2)	-0.44±5.13	0.377
R6	7.05±4.40	6.8 (3.6-9.6)	7.32±4.35	6.8 (4-10)	-0.26±3.90	0.489
R7	7.12±4.41	6.8 (3.6-9.2)	7.47±4.40	7.1 (4.4-10)	-0.35±3.85	0.354
p	[b]0.001**		[b]0.001**			
	Mean±SD	p	Mean±SD	p		
R1-R2	-0.73±2.10	[bb]1.000	-0.76±2.21	[bb]1.000		
R1-R3	-0.59±2.83	[bb]1.000	-1.18±2.79	[bb]0.807		
R1-R4	-1.74±3.88	[bb]0.906	-1.92±3.69	[bb]0.236		
R1-R5	-4.77±5.39	[bb]0.001**	-4.81±4.84	[bb]0.001**		
R1-R6	-8.10±5.07	[bb]0.001**	-8.32±5.08	[bb]0.001**		
R1-R7	-8.04±4.88	[bb]0.001**	-8.17±5.52	[bb]0.001**		

*[a]: Paired Samples-t test, [b]: Repeated Mesaures test, [bb]: Dunn-Bonferroni test, **p<0,01, *p<0.05, SD: Standart deviation,* R1: Central tooth region, R2: Lateral tooth region, R3: Canine tooth region, R4: First premolar tooth region, R5: Second premolar tooth region, R6: First molar tooth region, R7: Second molar tooth region

Right and Left Side

The difference between R1-R5, R1-R6 and R1-R7 bone heights was statistically significant (p<0,01). No significant difference was found in the other region comparisons (p>0.05) (Table 2).

Evaluation of Horizontal Measurements

Horizontal measurements at 1 mm depth: There was a statistically significant difference in the mean horizontal measurements on the left side compared to the right side in the R1 (p=0.005; p<0.01). In other regions, the changes in the horizontal measurements on the left side compared to the right side were not statistically significant (p>0.05) (Table 3).

Right side: The difference between R1-R5, R1-R6 and R1-R7 bone widths was statistically significant (p<0.01). No significant difference was found in other region comparisons (p>0.05) (Table 3).

Left side: The difference between R1-R6 and R1-R7 bone widths was statistically significant (p<0.01). No significant difference was found when comparing other regions (p>0.05) (Table 3).

Horizontal measurements at 3 mm depth: There was a statistically significant difference in the mean horizontal measurements on the left side compared to the right side in the R1 and R6 (p=0.001; p<0.01). In other regions, the changes in the horizontal measurements on the left side compared to the right side were not statistically significant (p>0.05) (Table 3).

Right side: The difference between R1-R5, R1-R6 and R1-R7 bone widths was statistically significant (p<0.01). No significant difference was found when comparing other regions (p>0.05) (Table 3).

Left side: The difference between R1-R6 and R1-R7 bone widths was statistically significant (p=0.001; p<0.01). No significant difference was found when comparing other regions (p>0.05) (Table 3).

Horizontal measurements at 5 mm depth: There was a statistically significant difference in the mean horizontal measurements on the left side compared to the right side in the R1 (p=0.005; p<0.01). In other regions, the changes in the horizontal measurements on the left side compared to the right side were not statistically significant (p>0.05) (Table 3).

Right side: The difference between R1-R7 bone widths was statistically significant (p=0.004; p<0.01). No significant difference was found when comparing other regions (p>0.05) (Table 3).

Left side: The difference between R1-R2 bone widths was statistically significant (p=0,007; p<0.01). No significant difference was found when comparing other regions (p>0.05) (Table 3).

Horizontal measurements at 7 mm depth: No statistically significant difference was found in the horizontal measurements of the left side compared to the right side in the regions (p>0.05) (Table 3).

Right side: No statistically significant difference was found between the horizontal measurements in the regions. (p>0.05) (Table 3).

Left side: The difference between R1-R2 bone widths was statistically significant (p=0.020; p<0.05). No significant difference was found in the other region comparisons (p>0.05) (Table 3).

Table 3. Comparison of horizontal measurements at 1, 3, 5 and 7 mm depth by party

Horizontal	Right maxilla Mean±SD	Right maxilla Median (IQR)	Left maxilla Mean±SD	Left maxilla Median (IQR)	Change	[a]p
1 mm						
R1	3.38±1.36	3.1 (2.3-4)	3.77±1.47	3.4 (2.7-4.4)	-0.39±1.39	0.005**
R2	3.23±1.34	2.9 (2.3-3.8)	3.37±1.21	3.2 (2.6-4)	-0.14±1.12	0.204
R3	3.65±1.22	3.5 (2.7-4.3)	3.75±1.43	3.6 (2.8-4.5)	-0.10±1.19	0.375
R4	3.61±1.34	3.4 (2.9-4.3)	3.83±1.45	3.8 (2.8-4.8)	-0.21±1.26	0.086
R5	3.88±1.51	3.7 (2.8-4.9)	4.29±1.38	4 (3.4-5.1)	-0.42±1.48	0.005
R6	4.76±2.10	4.4 (3.3-6)	4.95±1.84	5 (4-6.1)	-0.19±2.22	0.380
R7	5.42±2.29	5.2 (4-6.8)	5.41±2.26	5.2 (4.2-6.4)	0.01±2.24	0.975
p	[b]0.001**		[b]0.001**			
	Mean±SD	p	*Mean±SD*	p		
R1-R2	-0.16±0.98	[bb]1.000	-0.41±1.20	bb0.258		
R1-R3	0.27±1.22	[bb]0.419	-0.02±1.41	[bb]1.000		
R1-R4	0.23±1.40	[bb]1.000	0.05±1.64	[bb]1.000		
R1-R5	0.49±1.65	[bb]0.037*	0.52±1.67	[bb]0.081		
R1-R6	1.38±2.07	[bb]0.001**	1.18±2.17	[bb]0.001**		
R1-R7	2.04±2.37	[bb]0.001**	1.64±2.46	[bb]0.001**		
3 mm						
R1	4.26±1.57	3.9 (3.1-5.1)	4.74±1.54	4.5 (3.8-5.4)	-0.48±1.34	0.001**
R2	4.17±1.50	4 (3.1-5)	4.26±1.51	4 (3.2-5.3)	-0.09±1.09	0.410
R3	4.59±1.48	4.5 (3.4-5.6)	4.62±1.60	4.3 (3.4-5.6)	-0.03±1.27	0.835
R4	4.69±1.62	4.5 (3.6-5.8)	4.89±1.72	4.6 (3.7-6.1)	-0.20±1.34	0.133
R5	5.09±2.04	5 (3.7-6.4)	5.13±2.16	5.1 (4.1-6.4)	-0.04±1.87	0.834
R6	5.43±3.34	5.6 (4.1-7.6)	6.56±2.73	6.9 (5.6-8)	-1.13±3.24	0.001**
R7	6.64±3.48	7.3 (4.8-8.8)	6.83±3.21	7.6 (5.6-8.7)	-0.19±3.85	0.611
p	0.001**		0.001**			
	Mean±SD	**p**	**Mean±SD**	**p**		
R1-R2	-0.09±1.18	[bb]1.000	-0.48±1.12	[bb]0.140		
R1-R3	0.33±1.35	[bb]1.000	-0.12±1.40	[bb]1.000		
R1-R4	0.43±1.59	[bb]1.000	0.15±1.89	[bb]1.000		
R1-R5	0.83±2.08	[bb]0.002**	0.39±2.25	[bb]0.353		
R1-R6	1.17±3.28	[bb]0.001**	1.83±2.83	[bb]0.001**		
R1-R7	2.38±3.48	[bb]0.001**	2.09±3.28	[bb]0.001**		
5 mm						
R1	5.26±1.77	5.1 (4-6.1)	5.66±1.85	5.4 (4.5-6.8)	-0.40±1.56	0.010*
R2	4.87±1.79	4.6 (3.7-5.8)	4.98±1.85	4.7 (3.6-6.2)	-0.11±1.21	0.353
R3	5.27±1.61	5.2 (4.2-6.4)	5.46±1.77	5.2 (4-6.7)	-0.19±1.32	0.148
R4	5.41±2.02	5.5 (4-7)	5.70±1.93	5.4 (4.5-7)	-0.29±1.77	0.096
R5	5.33±2.90	5.4 (3.8-7.2)	5.47±2.98	5.8 (4-7)	-0.14±2.90	0.615
R6	5.39±4.28	6.6 (0-8.8)	5.40±4.21	7.2 (0-8.4)	-0.01±5.04	0.989
R7	5.72±4.56	7.1 (0-9.3)	6.16±4.43	7.6 (0-9.6)	-0.44±4.98	0.369
p	[b]0.001**		[b]0.001**			
	Mean±SD	**p**				
R1-R2	-0.39±1.35	[bb]1.000	-0.69±1.26	[bb]0.007**		
R1-R3	0.01±1.59	[bb]1.000	-0.20±1.62	[bb]1.000		
R1-R4	0.15±2.02	[bb]1.000	0.04±1.94	[bb]1.000		
R1-R5	0.07±2.90	[bb]1.000	-0.19±3.23	[bb]1.000		
R1-R6	0.13±4.33	[bb]0.402	-0.26±4.46	[bb]0.807		
R1-R7	0.46±4.67	[bb]0.004**	0.50±4.41	[bb]0.090		
7 mm						
R1	6.32±2.41	6.3 (4.8-7.6)	7.28±6.71	6.5 (5.3-8.2)	-0.96±6.38	0.127
R2	5.95±2.40	5.8 (4.4-7.2)	6.06±2.24	5.9 (4.6-7.3)	-0.11±1.97	0.566
R3	6.28±1.96	6.2 (4.8-7.6)	6.35±2.30	6.1 (5-7.8)	-0.07±1.48	0.615
R4	6.28±2.59	6.4 (4.9-8)	6.56±2.50	6.7 (5.2-8.1)	-0.28±2.73	0.303
R5	6.19±3.71	6.8 (4.6-8.6)	5.95±3.90	6.8 (3.9-8.4)	0.24±4.15	0.551
R6	4.79±5.00	4.8 (0-9)	4.61±4.87	2.4 (0-9.2)	0.18±5.95	0.757
R7	4.74±5.00	2.8 (0-9.2)	4.86±4.91	5.4 (0-10)	-0.12±4.59	0.783
p	[b]0.105		[b]0.038*			
	Mean±SD	**p**	**Mean±SD**	**p**		
R1-R2	-0.37±1.78	[bb]1.000	-1.22±6.40	[bb]0.020*		
R1-R3	-0.04±2.08	[bb]1.000	-0.93±6.63	[bb]1.000		
R1-R4	-0.04±3.00	[bb]1.000	-0.72±6.64	[bb]1.000		
R1-R5	-0.13±3.88	[bb]1.000	-1.33±8.11	[bb]1.000		
R1-R6	-1.53±5.15	[bb]1.000	-2.67±8.53	[bb]1.000		
R1-R7	-1.59±5.48	[bb]1.000	-2.42±8.61	[bb]1.000		

SD: Standart deviation, [a]: Paired samples-t test, [b]: Repeated mesaures test, [bb]:Dunn-Bonferroni test, *p<0.05, **p<0.01

Evaluation by Gender

The mean horizontal measurements of males at 3 mm depth were statistically significantly higher than those of females (p=0.006; p<0.01). The mean horizontal measurements of males at 7 mm depth were statistically significantly higher than those of females (p=0.014; p<0.05). Other horizontal and vertical measurements did not show statistically significant differences between the genders (p>0.05) (Table 4).

Evaluation by Age

There was a negative and weakly statistically significant correlation between patient age and mean vertical measurements (r=-0.300; p=0.002; p<0.01). There was no statistically significant correlation between patient age and mean horizontal measurements at 1, 3, 5 and 7 mm depth (p>0.05) (Table 5).

Table 4. Comparison of vertical and horizontal measures in regions by gender

		Male (n=42)	Female (n=62)	[a]p
Vertical	Mean±SD	11.82±2.79	11.94±3.04	0.850
	Median (min-max)	12.3 (6.2-16.3)	11.6 (4.4-22.8)	
Horizontal 1 mm	Mean±SD	4.44±1.18	4.22±2.89	0.647
	Median (min-max)	4.4 (2.7-7.6)	3.8 (1.9-25.5)	
Horizontal 3 mm	Mean±SD	5.60±1.61	4.82±1.22	0.006*
	Median (min-max)	5.7 (2.8-9)	4.7 (2.4-8)	
Horizontal 5 mm	Mean±SD	5.83±2.03	5.16±1.48	0.055
	Median (min-max)	6.1 (2-10)	5.2 (2.1-8.6)	
Horizontal 7 mm	Mean±SD	6.45±2.18	5.48±1.77	0.014**
	Median (min-max)	7 (2.7-10.8)	5.7 (0.4-9)	

[a]:Sudent-t test, SD: Standart deviation, Min: Minimum, Max: Maximum, *: p<0.05, **: p<0.01

Table 5. Relationship between vertical and horizontal measurements in regions by age

	Age	
	r	p
Vertical	-0.300	0.002*
Horizontal 1 mm	-0.025	0.800
Horizontal 3 mm	-0.088	0.374
Horizontal 5 mm	-0.032	0.748
Horizontal 7 mm	0.041	0.678

r: Pearson correlation test, *: p<0.05

DISCUSSION

In this study, the residual alveolar bone heights and widths of patients with complete maxillary edentulism were evaluated in 7 different tooth regions from anterior to posterior, from the central tooth region to the second molar tooth region. It was found that the bone height in the central tooth region was greater than that in the 2nd premolar, 1st molar and 2nd molar tooth regions. Farina et al.[18] determined the vertical bone resorption in the posterior aspect of the edentulous maxilla and found that the bone height was lower in the 2nd premolar, 1st molar and 2nd molar regions, similar to our study. Lekovic et al.,[19] Camargo et al.,[20] Pelegrine et al.[21] reported that vertical bone resorption after extraction varied between 11-22%. Similarly, Iasella et al.,[22] Barone et al.[23] and Aimetti et al.[10] showed that vertical bone resorption was greater in the buccal aspect of the socket at an average of 6 months after extraction. D'Souza,[16] Cawood and Howell[24] reported that alveolar bone resorption occurring one year after extraction was greater in the horizontal than in the vertical direction. These studies show that alveolar bone resorption continues actively during the first year after extraction. Studies have shown that bone resorption is faster and more extensive in the horizontal direction than in the vertical direction. When the results of the present study were evaluated in terms of the minimum bone height and width required for implant surgery, it was observed that horizontal bone resorption was higher than vertical resorption and, as a result, horizontal insufficiency was higher. In addition to physiologic bone resorption after extraction, this may have occurred as a result of traumatic or complicated tooth extraction in the patients included in the study. When the right and left sides were compared in this study, the regions with differences were the lateral region in terms of bone height, the central region at 1, 3 and 5 mm, and the first molar region at 3 mm in terms of bone width. Bone height and width were greater on the left side in these regions. In the study by Katsoulis et al.,[17] it was shown that there was no difference between the right and left side in terms of bone width measurements in different regions of the edentulous maxilla.[17] In the study by Katsoulis et al.,[17] measurements were taken at 3 and 8 mm, whereas in this study measurements were taken at 1, 3, 5 and 7 mm, and we believe that this is the reason for the difference. In addition, Katsoulis et al.[17] found that there was no difference in bone width between the genders in their study, whereas this study found that bone width was greater in males at 3 and 7 mm depth. The difference between sides in this study suggests that patients generally use their right side in these regions and resorption is more common. In addition, the right-sided teeth in these regions may have been lost earlier or tooth extractions in these regions may have been traumatic. Among the possible reasons, the possibility that patients use one side more when chewing suggests the negative effect of unilateral chewing on alveolar bone resorption as well as temporomandibular joint disorders. In addition, we think that the fact that people use their right side more when chewing may also be related to being right-handed and is a topic that needs to be investigated.

Ulm et al.[25] found that bone height in the edentulous posterior maxilla ranged from 3.23 to 9.3 mm. In this study, the mean bone height in the edentulous posterior maxilla between the 1st premolar and 2nd molar ranged from 7.05-13.73 mm. In contrast to the study by Ulm et al.,[25] the bone height in this study was higher. We believe that the reason for this difference is that the patients in this study had less resorption in the vertical direction and the mean age of the patients in this study was lower. There was also a negative relationship between age and bone height was found in this study. The fact that the mean age was higher and the bone heights were lower in the Ulm et al.'s[25] study compared to this study supports the negative relationship between age and bone height.

Padhye and Bhatavadekar[26] evaluated bone width in the edentulous posterior maxilla and reported that the incidence of bone width less than 6 mm was 55.03%. de Souza Nunes et al.[27] found this rate to be 16.3%. Both studies stated that horizontal bone augmentation is required for alveolar ridges less than 6 mm, taking into account 1-2 mm of healthy bone around dental implants. In contrast to these studies, when the average widths from the 1st to the 7th region at a depth of 1 mm are evaluated in this study, they vary between 3.23-5.42 mm and the average widths are 100% below 6 mm. This indicates that horizontal resorption was particularly severe in the patients included in the study and that the patients required a high rate of horizontal bone augmentation. Padhye and Bhatavadekar[26] found that bone widths in the edentulous maxillary premolar and molar regions were similar. In support of Padhye and Bhatavadekar's findings, this study found no difference between the bone widths of the edentulous premolar and molar regions. Pramstraller et al.[28] showed that the mean bone widths of edentulous sites at 1 mm depth were 4.9 mm for the 1st premolar, 4.8 mm for the 2nd premolar, 5.7 for the 1st molar and 6.6 mm for the 2nd molar. In this study, these widths were 3.61, 3.88, 4.76 and 5.41, respectively, and were found to be lower than in the study by Pramstraller et al.[28] Although the mean age in this study (50.88±10.28) was similar to that of Pramstraller et al.[28] (55.2±10.1), we believe that the main reason for the lower bone widths was early tooth loss and increased duration of

edentulism. Systemic deficiencies of which the patients were unaware, duration of complete edentulism, traumatic or complicated tooth extractions, dietary and chewing habits that may affect resorption, occlusion and bite conditions, and the use of removable dentures may have influenced the results. In addition, the mesiodistal widths of the teeth used as reference in the study may not be appropriate for each patient. The points determined for the patients' teeth may have deviated from their original positions. These were the limitations of the study.

CONCLUSION

This study was the first to compare residual bone height and width at 1, 3, 5 and 7 mm depth from the central region to the second molar region in individuals with complete maxillary edentulism. It was found that the regions with the least bone width were the central and lateral regions and the region with the least bone height was the first molar region. It was observed that the bone height was higher on the left side in the lateral region and the bone width at the 1st, 3rd and 5th mm in the central region was higher on the left side. These results showed that the loss of horizontal bone width as a result of ACR in edentulous patients was advanced and the need for horizontal augmentation was very high in this group of patients considered for dental implant surgery. We recommend that atraumatic extraction and socket protection methods, which are among the main factors causing this situation, should be popularised and that clinicians should be made aware of this issue.

ETHICAL DECLARATIONS

Ethical Committee Approval

The study was approved by the Non-interventional Ethics Committee of Van Yüzüncü Yıl University (Date: 17.03.2023, Decision No: 2023/03-09).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, conduct and analysis of the work, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1452696
J Health Sci Med. 2024;7(3):259-263

Investigation of the relationship between borderline personality organization and perceived abuse experiences in romantic relationships: moderating role of rejection sensitivity

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Cite this article as: Faraji H. Investigation of the relationship between borderline personality organization and perceived abuse experiences in romantic relationships: moderating role of rejection sensitivity. *J Health Sci Med.* 2024;7(3):259-263.

Received: 14.03.2024 ◆ **Accepted**: 14.04.2024 ◆ **Published**: 27.05.2024

ABSTRACT

Aims: The study aims to determine the moderator role of rejection sensitivity in the relationship between borderline personality organization and perceived abuse experiences in romantic relationships.

Methods: In this study, which has a relational screening model, participants were reached by convenience sampling. Participants consisted of 116 (30.1%) men and 270 (69.9%) women aged 18-45 (M=27.95±7.25), who participated in the study voluntarily. Data collecting tools are the socio-demographic data form, Borderline Personality Questionnaire (BPQ), Adulth Rejection Sensitivity Scale (ARSS), and Romantic Relationship Assessment Inventory (RRAI).

Results: It was concluded that rejection sensitivity has a moderating role in the relationship between borderline personality organization and perceived abuse experiences in romantic relationships. Also, it has been determined that a decrease in education level is associated with a higher level of borderline personality organization and perceived abuse experiences in romantic relationships.

Conclusion: Findings show that it may be beneficial to target rejection sensitivity in psychotherapeutic practices in order to prevent individuals with borderline personality organization from being harmed in romantic relationships and to increase their romantic relationship quality.

Keywords: Borderline personality organization, borderline personality disorder, rejection sensitivity, abuse, romantic relationships

INTRODUCTION

Borderline personality disorder (BPD) is a disorder characterized by variability in the individual's self, interpersonal relationships, affect, behavior, cognitive processes, and rejection sensitivity.[1,2] Romantic relationships are where maladaptive interpersonal functioning of BPD manifests itself most severely.[3] High levels of instability in their romantic relationships are frequently observed in them, as evidenced by their propensity to select partners who have mental health issues, low relationship satisfaction, high levels of interpersonal dependence, communication problems, and a history of physical and psychological violence.[3]

In cases where the prevalence and intensity of borderline personality traits are not high enough to disrupt the daily functionality of the individual, the existence of a borderline personality organization (BPO) is mentioned.[4] As the level of borderline personality traits increases, the probability of the individual being exposed to abuse increases.[5,6] Since borderline individuals believe that even their existence in the world is disturbing, they turn to more submissive attitudes in order to neutralize this discomfort and prevent rejection.[7,8] They have difficulty turning down the offer of sex.[9] Besides, their intolerance of separation makes individuals with BPO more susceptible to being in abusive relationships.[10] Individuals with borderline personality disorder have difficulty saying "no" and rejecting other people, even in harmful situations, due to their fear of being rejected and becoming face-to-face with emptiness. Their tendency to act focused on their partners' wishes and expectations and their difficulty in saying no become especially evident in romantic relationships.[11]

One of the world's most concerning societal issues is abuse in romantic relationships.[12] Researches show that adult abuse rates (especially sexual abuse) are significantly higher in BPD compared with other personality disorders. People with BPD are more prone to become intimate partner violence victims because their separation anxiety makes them unable to protect themselves from their partner's hazardous demands and attitudes.[10,13,14] Also, it is known that abuse experiences predict more severe clinical presentation and poorer prognosis of BPD, especially suicidality.[13] Therefore, the aim of the study is to investigate the relationship between borderline personality organization, abuse experiences, and rejection sensitivity.

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The central hypothesis of this study is that rejection sensitivity has a moderating role between borderline personality organization and perceived abuse experiences in romantic relationships. It is thought that the research results of the study may be helpful in the psychotherapy processes of people who report romantic relationship abuse. The results obtained may shed light on possible problems that individuals with borderline personality organization and rejection sensitivity may experience in their close relationships, especially in the romantic relationship area. They may encourage preventive psychotherapeutic studies to be carried out before romantic relationship abuse occurs.

METHODS

Permission to use the scales was obtained via e-mail from the researchers who developed the scales used in the study and conducted the validity and reliability studies of their adaptation to Turkish. Information was obtained about the scale items and scoring procedures. Then, an application was made to the İstanbul Aydın University Ethics Committee to evaluate whether the relevant study involved ethical violations. The study was carried out after obtaining the permission of the İstanbul Aydın University Social and Humanistic Sciences Ethics Committee (Date: 13.11.2023 Decision No: 2023/11). Since the necessity of protecting individual rights was prioritized in the research, the Helsinki Declaration of Human Rights was complied with throughout the study period. The scales were distributed to the participants along with the informed consent form through online platforms, and no identification information was collected from the participants to protect their privacy. It was stated that the personal information of the participants would not be shared with anyone other than the researchers and that they could leave the research at any time they wanted. It took an average of 20 minutes to fill out the scales.

This study was designed by the relational screening model. The relational scanning model determines the interaction between more than one variable. In the relational scanning model, the direction and level between variables are determined. Participants were reached through convenience sampling method from volunteer individuals living in Istanbul/Turkey.116 (30.1%) participants were men and 20 (69.9%) were women. 64 (16.6%) were high school graduates, 266 (68.9%) were university graduates, and 56 (14.5%) were graduates. The youngest participant is 18 years old, and the oldest participant is 45 years old, with an average age of 27.95±7.25.

Data Collection

Socio-demographic data form: The socio-demographic data form, prepared by the researchers for the purpose of the study, consists of age, gender, and education level questions.

Borderline personality questionnaire (BPQ): Poreh et al.[15] adapted it into Turkish by Ceylan.[16] Validity and reliability studies of this scale, which evaluates borderline personality traits according to DSM-IV criteria, have been conducted. This evaluation scale consists of a total of 9 subscales and 80 items. The internal consistency coefficient of the scale was obtained between 0.65 and 0.84, and the Cronbach's α value was found to be 0.94. Nine subscales of the scale; affective instability, impulsivity, abandonment, relationships, suicide/self-mutilation behavior, self-image, intense anger, feeling of emptiness, quasi- psychosis states.[16]

Romantic relationship assessment inventory (RRAI): The scale was developed by Kılınçer and Tuzgöl-Dost[17] to determine perceived abuse in romantic relationships. The five-point Likert-type scale consists of 70 items. The lowest score on the scale is 70, and the highest score is 350. The Cronbach Alpha reliability coefficient of RRAI was found to be .97. An increase in the score means that the abuse experienced in a romantic relationship increases.[17]

Adult rejection sensitivity scale (ARSS): The Scale was developed by Downey and Feldman[18] to measure the level of rejection sensitivity. Berenson et al.[19] developed the adult form of the Rejection Sensitivity Scale. The adult form of the Rejection Sensitivity Scale was adapted into Turkish by Bozkuş and Araz.[20] The scale is based on self-report and consists of 9 6-point Likert-type items. Two separate scores are obtained for each defined hypothetical situation: rejection and acceptance expectations. By inverting the acceptance expectation score and multiplying it by the rejection score, the rejection sensitivity score for that item is obtained. In their study, Bozkuş and Araz[20] found the Cronbach Alpha coefficient regarding the internal consistency of ARSS to be .62.

Statical Analysis

All statistical analyses of the study were performed using SPSS 27 software. In the first step, Cronbach Alpha coefficients were calculated to evaluate the reliability of the scales. As a result of these calculations, it was determined that the Cronbach Alpha values of all scales were above 0.70.[21] In the second stage, whether the scales showed normal distribution was meticulously examined. During this review process, it was observed that the kurtosis and skewness coefficients of the scales met the reference values between -2 and +2 specified by HahsVaughn and Lomax.[22] All these results show that it is appropriate to use parametric statistical tests in this research.

The level and direction of the relationship between the scales were evaluated using Pearson Correlation analysis. Additionally, to compare the scales according to demographic variables, an Independent Samples t-test was applied, and ANOVA was preferred. Process Macro 4.2 was used for regulatory role analysis. All these analyses were performed with a 95% confidence interval and a p-value of .05 as a reference.

RESULTS

According to Table 1, the kurtosis coefficient of the Romantic Relationship Assessment Inventory is 1.89, the skewness coefficient is 1.62, the kurtosis coefficient of the Adult Rejection Sensitivity Scale is 0.77, the skewness coefficient is 0.69, the kurtosis coefficient of the Borderline Personality Questionnaire is 0.01, the skewness coefficient is 0.97.

Table 1. Descriptive statistics and examination of kurtosis and skewness coefficients and cronbach alpha values of romantic relationship assessment inventory, adult rejection sensitivity scale and borderline personality questionnaire

	n	Min	Max	X	SD	kurtosis	skewness	(α)
Romantic relationship assessment inventory	386	70	139	83.93	17.24	1.83	1.62	0.94
Adult rejection sensitivity scale	386	18	96	39.96	14.58	0.77	0.69	0.86
Borderline personality questionnaire	386	6	62	23.42	15.14	0.01	0.97	0.95

Min: Minimum, Max: Maximum, SD: Standart deviation

The internal consistency coefficient, Cronbach's Alpha coefficient, was found to be 0.94 for the Romantic Relationship Assessment Inventory, 0.86 for the Adult Rejection Sensitivity Scale, and 0.95 for the Borderline Personality Questionnaire.

When Table 2 is examined, there is a moderate positive correlation between the scores of the Borderline Personality Scale and the Romantic Relationship Evaluation Scale (r=30, p<0.01).

Table 2. The relationship between perceived abuse experiences in romantic relationships, rejection sensitivity, and borderline personality organization

	1	2	3
1. Romantic relationship assessment inventory	1		
2. Adult rejection sensitivity scale	.01	1	
3. Borderline personality questionnaire	.30**	.11*	1

**p<0.01, *p<0.05 Name of the test applied: Pearson Correlation Test

A low-level positive correlation was found between the Borderline Personality Scale and Rejection Sensitivity Scale (r=11, p<0.05) scores.

When the findings of Table 3 show borderline personality traits do not have a predictive effect on abuse in romantic relationships (B=0.02, p>0.05), rejection sensitivity has a predictive effect on abuse in romantic relationships (B=-0.21, p<0.05), and the interaction variable is a significant predictor. It was determined that (B=0.08, p<0.05). It was concluded that rejection sensitivity has a moderating role in the relationship between borderline personality traits and abuse in romantic relationships.

Table 3. Examining the moderating role of adulth rejection sensitivity in the relationship between borderline personality organization and perceived abuse experiences in romantic relationships

Model	B	SH	T	P	Lower bound	Upper bound
(Constant)	84.13	4.28	19.64	<.001***	[75.71,	92.55]
Borderline personality organization	0.02	0.16	0.13	0.894	[-0.29,	0.34]
Adult rejection sensitivity	-0.21	0.10	-2.06	0.040*	[-0.42,	-0.01]
(BPO)*(ARS)	0.08	0.00	2.18	0.030*	[0.00,	0.02]
R^2=.10, F=14.76, p<.001***						

***p<.001, **p<.01, *p<.05 test used: PROCESS Macro 3.5

The change in the relationship between borderline personality traits and perceived abuse experiences in romantic relationships for different levels of rejection sensitivity (low, medium, or high) is presented in Figure.

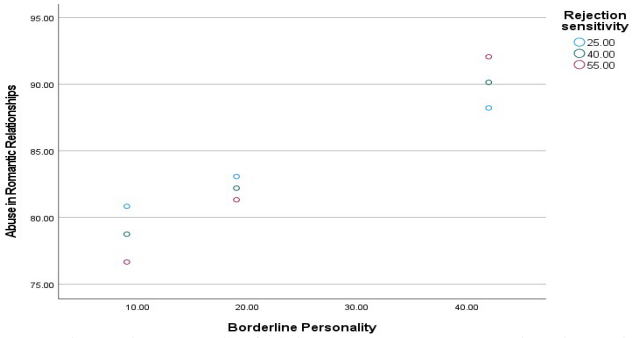

Figure. The moderating role of adult rejection sensitivity in the relationship between borderline personality organization and perceived abuse experiences in romantic relationships

According to the Figure, it has been observed that for different levels of rejection sensitivity (low, medium, or high), if borderline personality traits increase, the level of perceived abuse in romantic relationships increases.

According to Table 4, when the scores obtained from the Adult Rejection Sensitivity Scale were evaluated according to educational status, no significant difference was detected between the groups (p>.05).

Table 4. Comparison of perceived abuse experiences in romantic relationship, adulth rejection sensitivity and borderline personality organization in romantic relationships by educational degree

	Educational status								
	High school graduate[1] (n=64)		Graduate[2] (n=266)		Post graduate[3] (n=56)				
Dependent variables	X	SD	X	SD	X	SD	F(2,383)	p	Post-Hoc
Romantic relationship assessment inventory	89.19	20.56	82.75	16.27	83.50	16.82	3.66	0.027*	1>2
Adult rejection sensitivity scale	43.50	18.39	39.35	13.02	38.79	16.33	2.31	0.100	-
Borderline personality questionnaire	30.63	17.21	20.91	13.72	27.14	15.96	13.40	<001***	1,3>2

SD: Standart deviation, ***p<.001, **p<.01, *p<.05 test used: one-way analysis of variance (ANOVA)

When the scores from the Romantic Relationship Evaluation Scale [F(2.383)=3.66, p<.05] are examined according to educational status, the results of the Games-Howell findings show that high school graduates have significantly higher scores than university graduates.

When their scores from the Borderline Personality Questionnaire [F(2.383)=13.40, p<.05] were examined according to educational status, a significant difference was detected between the compared groups. The results of the Games-Howell findings show that those with high school or master's degrees received significantly higher scores than those with university degrees.

DISCUSSION

The central hypothesis of this study was confirmed that rejection sensitivity has a moderating role between borderline personality organization and perceived abuse experiences in romantic relationships. According to the findings, the increase in the level of rejection sensitivity strengthens the relationship between borderline personality organization and perceived abuse in romantic relationships.

Dutton[23] has a nested ecological theory on partner violence, which has a loss of common risk factors with BPD, including having BPD itself in the ontogenetic layer. This theoretical approach examines various environmental factors, emphasizing that IPV is a multidimensional issue. The macrosystem, which focuses on the society in which the victim lives and includes factors like age, education, employment, financial stress, length of relationship, marital status, number of children, previous arrest, spirituality, and social support, is the first level of Dutton's[23] nested ecological model.[23,24] Similarly, a current study indicates BPO levels become higher when individuals have lower educational degrees, which contributes to unemployment and financial stress. Their romantic relationship lengths are shorter than healthy individuals, and they perceive less social support.[25] The exosystem, or social structures in the victim's life, is examined at the second level.[14] This level has lots of common points with BPD, including abuse in past relationships, infidelity, childhood abuse, emotional abuse perpetration/victimization, jealousy, relationship communication, relationship satisfaction, separation, trauma, victim of forced sex, witness intimate partner violence (IPV) in family origin.[4,10,25-27] The microsystem level of Dutton's model[23] includes BPD itself as a risk factor for partner IPV, and other risk factors of this level are also the most seen components of BPD.[14] These components include alcohol use, substance use, anger, anxious attachment, self-blame, depression, PTSD, impulsivity, low self-esteem, and self-harm tendencies.[11]

Rejection sensitivity is a predictor of IPV victimization, including unwanted sexual contact and rape.[7] It predicts IPV victimization through self-silencing. It has been revealed that those with high rejection sensitivity are more likely to ingratiate themselves to a partner, pursue relationships that their support networks disapprove of, and engage in undesirable and unprotected sex in order to escape rejection.[28] According to Inman and London's[7] research, when violence or aggressiveness is used as a means of threatening rejection, people with high rejection sensitivity may also participate in self-silencing or ingratiating behaviors. People with borderline personality organization have fears about being rejected, and they are susceptible to engaging in self-silencing kind of behaviors and attitudes.[7-11]

On the other hand, low tolerance to rejection may also lead to IPV victimization. Borderline individualss who encounter stressors exhibit impulsivity in order to get rid of the tension, and impulsivity can lead to possible victimization experiences.[29] The feeling of worthlessness is one of the central emotions in borderline personality disorder.[7,8,11] Therefore, each encounter with the other triggers the sensitivity of rejection, and, subsequently, the feeling of worthlessness, and the resulting stress leads the individual to impulsivity.[29,30] Individuals diagnosed with borderline personality disorder are more prone to show signs of increased sexual obsession, to participate in sexual activity earlier in life, to be in casual relationships, to be promiscuous, and to have more than one sexual partner, as well as to have homosexual experiences. Individuals with borderline personality disorder also report being forced to have sex more often, being subjected to date rape or rape by a stranger, and more sexually transmitted diseases. In general, psychological themes related to sexual behavior in borderline personality disorder appear to be characterized by impulsivity and victimization.[10,13,14,26,29,30]

CONCLUSION

In conclusion of this study, it was determined that rejection sensitivity is an essential factor that strengthens the relationship between borderline personality traits and perceived abusive experiences in romantic relationships. The results do not suggest that people with high BPO and rejection sensitivity provoke violent behavior in their romantic relationships. As a matter of fact, BPO and rejection sensitivity might be best understood as risk factors as opposed to a causation component. Achieving even limited change in all aspects of a personality organization is not always possible. Where possible, it requires a long time and material and moral effort. However, romantic relationships are the area where borderline individuals have the most difficulty.[25] Besides, those who engage in IPV practices probably look for partners who seem receptive to rejection or eager to become friends.[7] In this regard, the current study findings show that it may be beneficial to target rejection sensitivity in psychotherapeutic practices in order to prevent individuals with BPO from being harmed in romantic relationships and to increase their romantic relationship quality. In addition, it has been determined that a low education level is associated with both borderline personality traits and increased exposure to abuse in romantic relationships. This result shows that education, which determines the individual's awareness, economic independence, level, and environment, can also be considered a preventive mental health service. One of the limitations of the study is that the sample group consists of individuals with borderline characteristics, not individuals diagnosed with borderline personality disorder. In light of studies in the literature, it has been observed that rejection sensitivity is associated with exposure to abuse in romantic relationships through self-silencing. In this regard, it is recommended that self-silencing be included in future studies.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of İstanbul Aydın University Social and Humanistic Sciences Ethics Committee (Date: 13.11.2023, Decision No: 2023/11).

Informed Consent

All participants saw the informed consent form on their screen and confirmed by clicking before answering scales.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The author has no conflicts of interest to declare.

Financial Disclosure

This study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1459785
J Health Sci Med. 2024;7(3):264-269

The effects of laparoscopy-guided transversus abdominis plane (TAP) block in the sleeve gastrectomy procedure: a randomized double-blinded placebo-controlled trial

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Cite this article as: Bük ÖF, Ocak S, Uyanık MS, et al. The effects of laparoscopy-guided transversus abdominis plane (TAP) block in the sleeve gastrectomy procedure: a randomized double-blinded placebo-controlled trial. *J Health Sci Med.* 2024;7(3):264-269.

Received: 27.03.2024 ◆ **Accepted**: 14.04.2024 ◆ **Published**: 27.05.2024

ABSTRACT

Aims: Laparoscopy-guided transversus abdominis plane (TAP) block is a novel postoperative analgesic modality. We aimed to explore the effect of TAP block in laparoscopic sleeve gastrectomy (LSG) procedures.

Methods: Forty patients were randomized into two groups: TAP block with bupivacaine and placebo. Visual analog scale scores at postoperative hours 1, 6, 12, and 24, total analgesic consumption and opioid doses, and postoperative nausea and vomiting (PONV) scores were evaluated between the groups.

Results: Postoperative first-hour VAS scores differed significantly between the groups ($p<0.05$). PONV scores were also lower in the TAP block group ($p<0.05$). The first rescue opiod requirement was later in the TAP block group than in the placebo group. Pain scores at postoperative hours 6, 12, and 24 and total analgesia doses were not significantly different between the groups.

Conclusion: Laparoscopy-guided TAP block reduced early postopeative pain and may also attenuate PONV in LSG.

Keywords: Sleeve gastrectomy, transversus abdominis plane block, postoperative pain management

Main points:

-Pain management after bariatric surgery is a challange.

-TAP block with bupivacain can decrease postoperative pain.

-TAP block can be performed by laparoscopy guidance.

INTRODUCTION

Laparoscopic sleeve gastrectomy (LSG) stands out as the bariatric procedure that is performed most often.[1-3] LSG has not only been found to be relatively easy to perform compared to other complex bariatric procedures, such as gastric bypass and duodenal switch, but it has also demonstrated effectiveness in achieving sustainable weight loss in prior studies.[1-4] However, despite the frequent performance of LSG, the management of postoperative pain and nausea-vomiting is still challenging. Paracetamol and non-steroidal anti-inflammatory agents are widely used for postoperative pain management, although opioid-based analgesia is usually required for rescue analgesia. However, opioids can also exhibit some severe adverse effects, including respiratory depression, nausea and vomiting, ileus, and even addiction.[5-8]

Achieving adaquate analgesia is essential in bariatric surgery since early mobilization is mandatory for preventing thromboembolic events in these patients.[9] Conventional analgesia modalities may not be sufficient, and other forms of analgesia are required for patients undergoing bariatric surgery. The transversus abdominis plane (TAP) block is a regional analgesia technique introduced by Rafi in 2001. It involves blocking the plane between the internal oblique muscle and transversus abdominis muscle through the infiltration of local anesthetic agents.[10] Many studies have demonstrated the effectiveness of TAP block in reducing postoperative pain as well as postoperative nausea and vomiting (PONV) in a range of abdominal surgery procedures, including both laparoscopic and open surgeries.[11-16] Various authors have investigated TAP block anesthesia in LSG, and conflicting results have been reported in randomized controlled studies. Some studies have suggested adjusting TAP block into a multimodal analgesia procedure, but others found no significant improvement with the technique.[17-20]

The aim of this study was to explore the impact of laparoscopy-guided TAP block on pain levels and other postoperative outcomes among patients undergoing primary LSG procedures.

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METHODS

Trial Design

This prospective randomized, placebo–controlled single-blinded study was conducted at the Samsun Health Sciences University Training and Research Hospital General Surgery Department following the receipt of local ethical committee approval (Date: 27.08.2020, Decision No: 2020/7/2). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Preoperative written informed consent was obtained from all participants, and the study was registered at www.clinicaltrials.gov (ID no. NCT05447429).

Patient Selection and Sample Size

Patients aged between 18 and 65 years who were scheduled for elective LSG were eligible for inclusion in the study. Exclusion criteria consisted of allergy to bupivacaine, presence of chronic pain or ongoing pain management, and an ASA classification of 4 or higher. Patients undergoing concurrent surgical procedures such as cholecystectomy, hiatal hernia repair, or abdominal hernia repair were also excluded. We also intended to remove patients experiencing postoperative complications requiring surgery or endoscopic interventions from the analysis. Using G-Power software power analysis, 40 participiants were enrolled into the study (20 patients for each group) to achieve 95% power, a two-sided 5% significance level, and a 1.45 impact size.

Groups and Randomization

We randomly assigned the 40 patients into two groups: a TAP block group (TAP-B) and a placebo group, with each group comprising 20 patients. Randomization was carried out using the sealed envelope method. Forty small pieces of paper with either TAP-Block or Placebo written on them were prepared and placed into non-transparent envelopes. Before each operation, the sealed envelopes were shuffled and one was selected by a blinded resident (MSU) and given to the surgeons (SO, ÖFB). These opened the envelope and performed either TAP-B or placebo, accordingly. The patient and the resident who collected those data (SO) were blinded to which procedure was performed, and double-blinded randomization was thus achieved.

Surgical Procedure and TAP Block Intervention

All procedures were conducted by two experienced bariatric surgeons (SO and ÖFB). Initially, the patient was positioned supine. After insufflation using a Veress needle inserted into the left subcostal region, a 10-mm camera trocar was placed on the left side of the umbilicus. With direct visualization, 15 ml of 0.5% bupivacaine +5 ml of saline or 20 ml of saline (as a placebo) were bilaterally administered at a single point in the transversus abdominis plane. The needle puncture was made in the midaxillary line between the subcostal margin and iliac crest once the needle tip was identified just above the peritoneum, and then the syringe was retracted. The accurate injection site was confirmed by observing peritoneal bulging due to the injected agents (Doyle's bulge), which the surgeons observed in all cases (Figure 1).

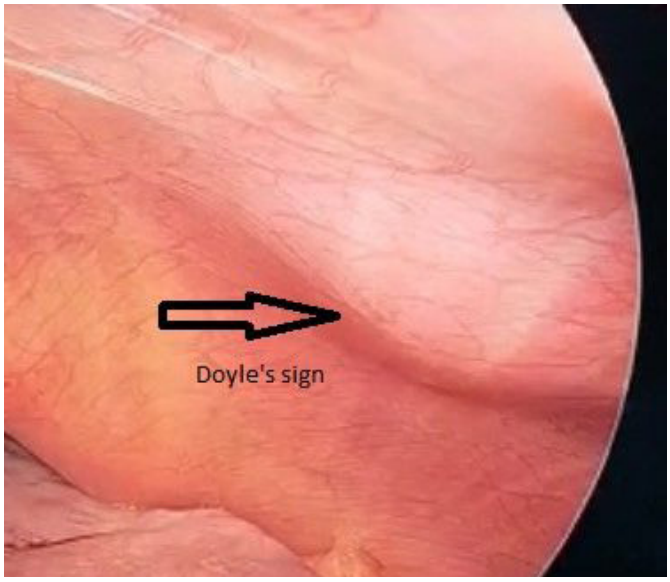

Figure 1. Doyle's sign

After the TAP-B procedure, a 10-mm trocar was inserted into the left anterior axillary line, and the other trocars (5-mm and 12-mm) were placed in the right midclavicular line as shown in Figure 2. A liver retractor was used routinely to achieve a clear view of the hiatus. Bipolar energy devices (LigaSureTM Medtronic, Covidien product, Minneapolis, MN, USA) were utilized to devascularize the greater curvature of the stomach up to the left crus, approximately 4-6 cm away from the pylorus. Subsequently, a 36 F bougie was introduced, and sleeve gastrectomy was performed. Following the methylene blue leak test, the resected stomach was extracted from the abdomen. Trocars were removed under direct observation, and the procedure was concluded.

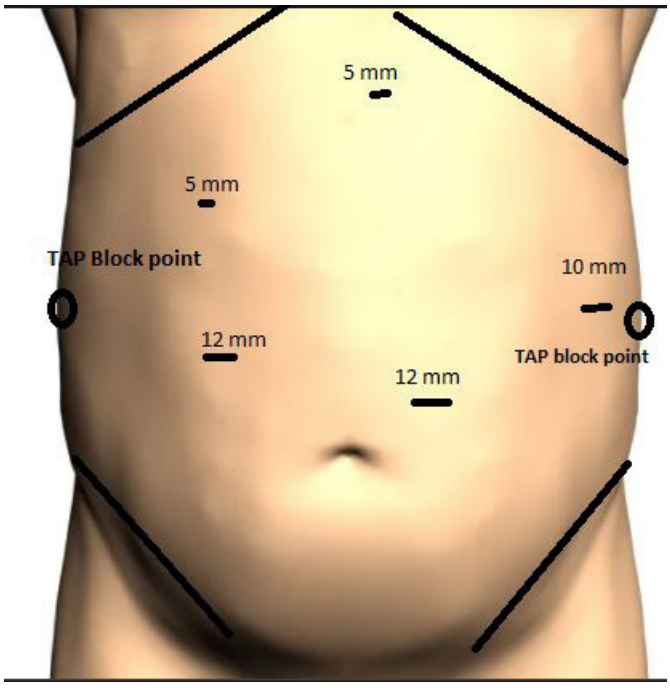

Figure 2. Trocar sites and TAP block injection site

Paracetamol 1000 mg was administered intravenously twice daily to both groups, and no opioids were administered during the perioperative course or in the postoperative

anesthesia care unit. Opioid-derived drugs (tramadol) were only given for rescue analgesia. Metoclopramide 10 mg was routinely administered three times per day to all patients as an antiemetic in the postoperative period. Patients were allowed to liquids on postoperative day 1 and were discharged on postoperative days 3 or 4.

Outcomes

The primary outcomes of this trial were to assess the patients' visual analog scale (VAS) scores at postoperative hours 1, 6, 12, and 24 together with postoperative analgesic doses.

Secondary outcomes included first mobilization and flatus times after surgery, nausea and vomiting scores, the times of first opioid administration, and operative times. PONV scores were calculated with the PONV scale as described in various previous studies. PONV scores were categorized as follows: 0 for no nausea or vomiting, 1 for mild nausea not requiring medication, 2 for moderate nausea requiring medication, and 3 for severe nausea and/or vomiting.[21-23]

Statistical Analysis

SPSS software was utilized for statistical analysis. Chi-square tests were employed for categorical variables analysis, while either the Mann-Whitney U test or Student's t-test was applied to compare mean values between the groups following the Shapiro-Wilk normality test. p-values <0.05 were considered statistically significant.

RESULTS

The study flowchart is shown in Figure 3. The 40 patients were randomly assigned into two equal groups. All the participants were subjected to analysis, and no patients were excluded from the study. Preoperative variables including age, BMI, and sex were similar between the groups and exhibited no significant differences. The groups' preoperative data are summarized in Table 1. No intraoperative complications developed, and all patients were transferred to the surgery ward, as expected. Postoperative courses were uneventful, and no major complications occurred.

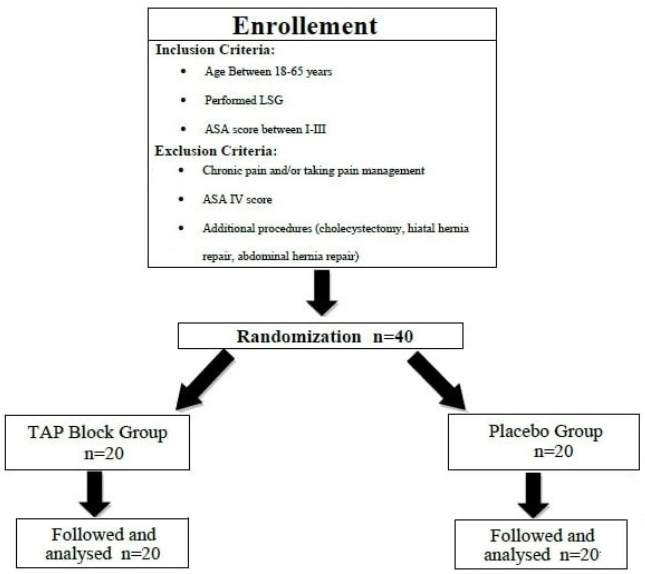

Figure 3. Study flowchart

Table 1. Patients' preoperative characteristics

	TAP-B	p	Total	p value
Age±SD (Min-Max)	33±9 (21-56)	30.9±9.14 (19-52)	31.95±9.03 (19-56)	0.409
BMI±SD (Min-Max)	44.6±3.37	46.12 ±6.24	45.36±5.01	0.776
Sex				
Male (%)	2 (10%)	5 (25%)	7 (17.5%)	
Female (%)	18 (90%)	15 (75%)	33 (82.5%)	0.212
Total	20	20	40	

TAP-B: Transversus abdominis plane block, p: Placebo, SD: Standart deviation, BMI: Body mass index, Min: Minimum, Max: Maximum

A statistically significant difference was observed in terms of pain scores between the two groups during the first hour after surgery (p<0.05). However, pain scores at hours 6, 12, and 24 exhibited no significant differences. Mean and p values are shown in Table 2. The total doses of postoperative paracetamol or opioids did not differ significantly between the groups. Times to the first opioid administration differed significantly between the groups (p<0.05), with patients in the TAP-B group receiving rescue opioids later than the placebo group (286.25 minutes vs 217.22 minutes, respectively). Additionally, two patients in the TAP-B group did not require opioids. Nausea-vomiting scores were significantly lower in the TAP-B group compared to the placebo group (p<0.05). There were no significant differences observed in first flatus times, first mobilization times, or operative times between the groups. The findings of the groups are summarized and compared in Table 2.

Table 2. Postoperative data for the study groups

	TAP-B	p	p value
Operation time-min (SD)	68 (18.73)	71.8 (15.11)	0.485*
Time till the first opioid administration-min (SD)	286.25 (117.67)	217.22 (83.22)	0.046*
VAS Score-1. hour (SD)	8.25 (1.11)	9.2 (1.19)	0.009¥
VAS Score-6 (SD)	5.8 (1.98)	6.15 (1.78)	0.562¥
VAS Score-12 (SD)	3.75 (2.02)	4.05 (2.03)	0.591¥
VAS Score-24 (SD)	2.10 (1.25)	2.05 (1.46)	0.723¥
Nause-vomiting score (SD)	2.15 (0.67)	2.70 (0.57)	0.006¥
Total tramadol dose-mg (SD)	170 (47.01)	195 (123.43)	0.431¥
Total parasetamol dose-mg (SD)	2000 (324.44)	2350 (745.16)	0.085¥
Flatus time-hour (SD)	13.95 (5.68)	13.50 (5.73)	0.828¥
Mobilization time-hour (SD)	14.90 (8.67)	19.20 (7.11)	0.119¥

TAP-B: Transversus abdominis plane block, p: Placebo, SD: Standart deviation, *Student t-test, ¥: Mann-Whitney U test, VAS: Visiual analog scale

DISCUSSION

Postoperative pain management in bariatric surgery continues to pose a challenge for surgeons. Effective pain control allows earlier mobilization, which plays a crucial role in preventing venous thromboembolism, as reported in previous studies.[9,24] Opioids are commonly used in postoperative pain management regimens in almost all types of surgery.[25] However, despite their analgesic efficacy, they also cause a number of adverse effects, including nausea and vomiting, respiratory depression, constipation, and hypotension.[26] Opioid addiction is another problem, with up to 10% patients exhibiting opioid addiction after bariatric surgery, meaning that their use should be as limited as possible.[27-29]

We set out to investigate whether the TAP-B procedure can reduce pain and opioid consumption following LSG. While a

notable distinction was observed in the VAS scores between the two groups at the initial postoperative hour, no significant variances were noted at 6, 12, or 24 hours. The total opioid and paracetamol doses showed no significant differences as well, although the TAP-B group experienced a longer interval before the first opioid administration compared to the placebo group. Additionally, two patients in the TAP-B group did not require any opioid administration. However, these data did not support the idea that TAP block with bupivacaine exhibits a favorable effect on postoperative pain management. Previous research has investigated the impact of TAP block on pain management in bariatric surgery, with several authors noting reduced postoperative pain, decreased analgesic needs, shorter hospital stays, and earlier resumption of daily activities as a result of this block.[18,19,30-35] In contrast, however, Wong et al.[20] and Saber et al.[17] observed no significant reduction of postoperative pain or opioid consumption after bariatric surgery. The variation in these studies may be attributed to several factors. Firstly, differences in the TAP Block application can vary among practitioners. Variances in the application site and doses of administered anesthetic agents may have influenced the outcomes. Another reason is the disparity in analgesia protocols applied during the perioperative period and diverse practices in Laparoscopic Sleeve Gastrectomy (LSG), such as changes in the number of ports, materials or techniques used to reinforce the stapler line (e.g., omentopexy, suturing to reinforce the stapler line), may lead to alterations in postoperative pain levels. Lastly, variations in patients' pain thresholds can also impact the results of the studies. Also the ineffectiveness of the intervention was attributed to enhanced recovery after surgery already improving postoperative pain, with the TAP block procedure therefore producing no additional benefit.[20]

The TAP block procedure can be conducted using either ultrasound guidance (USG) or laparoscopy. Several previous studies, along with a recent meta-analysis, have indicated that laparoscopy-guided TAP block is equally effective compared to USG-guided TAP block.[11,12,14,36-38] Laparoscopy-guided TAP block provides a clear field of vision through direct visualization of the peritoneum, thus avoiding the risk of intra-abdominal organ injury. In addition, USG-guided TAP block entails a longer operative time and requires expensive equipment and advanced radiological skills. It can be particularly difficult to identify true anatomical landmarks using USG in obese patients due to a thick layer of subcutaneous adipose tissue, and laparoscopy-guided TAP block may therefore be safer in these cases. Although Mittal et al.[30] concluded that USG-guided TAP block is a practicable and effective technique, other authors suggest that obesity poses a challenge for that technique.[19,39,40] We therefore prefer the laparoscopy-guided TAP block in obesity surgery at our clinic.

PONV represents another challenge in bariatric surgery and can be seen in approximately half of patients.[41-43] In agreement with previous studies, the current study observed lower postoperative nausea and vomiting (PONV) scores in the TAP-B group.[30,31]

Limitations

There are two major limitations to this study that need to be addressed. First, the number of patients was quite low, despite the sample size being calculated using power analysis. The effects of TAP Block application on pain management during Laparoscopic Sleeve Gastrectomy (LSG) can be better understood through the planning of advanced studies involving a larger number of patients. Second, although the VAS scale is a well-validated pain assesment tool, pain is a subjective phenomenon based on self-evaluation. Furthermore, in this study, only the immediate postoperative effects of TAP Block application were investigated, and no conclusive findings regarding its long-term outcomes were reached. However, the fact that the patients and assessors were blinded in this study that enhances the power of the trial.

CONCLUSION

Laparoscopic-guided TAP-B with bupivacaine resulted in a small decrease in pain at the postoperative first hour after LSG and improved PONV. The study recommends incorporating TAP block into the postoperative analgesia protocol after LSG. However, further trials with larger sample sizes are necessary to better understand its effects on pain management and postoperative nausea and vomiting (PONV).

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Samsun Health Sciences University Training and Research Hospital Clinical Researches Ethics Committee (Date: 27.08.2020, Decision No: 2020/7/2).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1453520
J Health Sci Med. 2024;7(3):270-277

Electrocardiographic changes of patients who were under the rubble and were admitted to the hospital during Kahramanmaraş Earthquake

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Cite this article as: Akkaya S, Çakmak Ü. Electrocardiographic changes of patients who were under the rubble and were admitted to the hospital during Kahramanmaraş Earthquake. *J Health Sci Med.* 2024;7(3):270-277.

Received: 15.03.2024 ◆ **Accepted**: 17.04.2024 ◆ **Published**: 27.05.2024

ABSTRACT

Aims: In this study, we aimed to determine the electrocardiographic findings in earthquake victims who were admitted to our hospital after the Kahramanmaraş earthquake.

Methods: We included all patients who applied to Diyarbakır Gazi Yaşargil Training and Research Hospital as earthquake victims in the study. The total number of injured patients removed from the rubble after the earthquake and admitted to our hospital was 321. A total of 139 patients were admitted to our hospital for examination and treatment. Fourty of them have a electrocardiograhphy. Clinical characteristics of the patients were compared according to the presence of crush syndrome. Patients who received further treatment in the intensive care unit (ICU) were compared with patients who did not require intensive care in terms of clinical characteristics. Electrocardiograpghy (ECG) findings were presented in all groups.

Results: Crush syndrome developed in 45% of patients, while 25% developed acute renal failure. As expected, compartment syndrome was more common in patients with crush syndrome (66.7% vs 18.2%, p=0.002). The proportion of patients requiring dialysis treatment was 12.5% (n=5). The proportion of patients who received further treatment in the intensive care unit was 35% (n=14). In terms of ECG characteristics, heart rate was higher in ICU-treated patients (105/min vs 86/min, p<0.001), PR interval was longer in ICU-treated patients (0.2 s vs 0.14 s), QRS complex was shorter in ICU-treated patients (0.05 mm vs 0.077 mm, p=0.021). QT interval was shorter in patients who admitted to intensive care unit (0.33 vs 0.35, p=0.021). In patients with crush syndrome, PR interval was longer (0.17 vs 0.16, p=0.006), QRS width was shorter (0.06 vs 0.072, p=0.021). In addition, the T-amplitude in the ECG was found to be higher in those who developed acute kidney injury compared to those who did not (0.20 vs. 0.10, p=0.018). Again, the T-amplitude was higher in those who required dialysis treatment (0.20 vs. 0.10, p=0.009).

Conclusion: In this study, we demonstrated some possible ECG changes such as PR prolongation and narrow QRS in earthquake victims admitted to our hospital. ECG can be used as a simple but predictive tool to monitor cardiovascular outcomes in earthquake victims.

Keywords: Crush syndrome, electrocardiography, electrocardiographic findings

INTRODUCTION

On February 6, 2023, two earthquakes of magnitude 7.8 Mw (±0.1) and 7.5 Mw occurred at 04:17 and 13:24, nine hours apart, with the epicenter in the Pazarcık and Ekinözü districts of Kahramanmaraş. Many houses were destroyed after the earthquake, so according to official figures, 50,785 people lost their lives and 108,000 citizens were rescued from the rubble with injuries.[1] The people who were trapped under the rubble after the earthquake and survived had to deal with severe organ injuries, bleeding, bruising, crush syndrome and multiple organ failure related to crushing. Those who lived in the area where the earthquake occurred and who were rescued from the rubble, as well as their relatives, faced a huge housing problem and there was a large exodus. The housing and other stressful situations caused by the earthquake and after the earthquake affected people's biopsychosocial situation and caused disturbances.

After the earthquake, an earthquake relief committee was set up for the injured who were rescued from the rubble and taken to the Diyarbakır Gazi Yaşargil Training and Research Hospital. This committee included specialists in cardiology, nephrology, internal medicine, emergency medicine, orthopedics, general surgery, anesthesia and intensive care. Numerous metabolic parameters of the earthquake victims who were admitted to our hospital were examined. The treatment process for the injured hospital patients was based on these metabolic values. ECG monitoring was carried out to monitor the patients who were dehydrated under the rubble,

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transferred to our hospital and admitted as inpatients. An attempt was made to determine the presence of cardiac effects based on the developing parameters in the ECG. We also wanted to investigate the relationship between the changes in the ECG of the patients and the consequences of muscle contusion in the patients, the length of hospitalization of the patients, the need for admission to the intensive care unit, the length of stay of the patients, the results of contusion syndrome, the number of amputations, the duration of infection treatment and mortality.

Victims trapped under rubble during earthquakes are forced to remain in narrow piles of rubble in an oxygen-free environment for a long time. People trapped under the rubble suffer muscle contusions in various parts of the body. As a result of muscle contusions, there may be excessive calcium release from the muscle cell, intense release of oxygen radicals, lipid peroxidation and increased interaction between PMN and endothelium, which can affect and even injure the heart. In addition, the destruction of muscle cells leads to an increase in potassium levels (K+). Hypovolemia occurs because earthquake victims who lie under the rubble for a long time remain hypoxic under the rubble and do not consume food or drink for a long time. The physiopathological condition that results from all these reasons can also lead to problems in the heart muscle. The simplest medical method that can show us doctors the possible pathologies that can develop in the heart muscle is the ECG. The potassium, calcium, hypoxia and hypovolemia environments mentioned above alert us by causing changes in the P wave, QRS wave and T wave on the ECG.[2]

The earthquake itself and the long stay under rubble can also cause changes in the autonomic nervous system of people. The people trapped under the rubble are under severe stress. This affects the heart rate and heart rhythm in different ways via the autonomic nervous system. The autonomic nervous system affects the heart: Due to the different autonomic innervations in people trapped under rubble, stimulation of the sympathetic and parasympathetic nervous systems can have different effects. Stress increases sympathetic tone and subsequently decreases parasympathetic activity, which can trigger supraventricular arrhythmias and also lead to the development of life-threatening ventricular arrhythmias. The increase in certain electrolytes in the blood due to muscle breakdown and asymmetric innervation caused by stress in the autonomic nervous system affects the heart muscle and causes cardiac arrhythmias. Most sudden deaths that occur during and after the earthquake are attributed by clinicians to renal causes. However, there may also be deaths due to sudden cardiac arrhythmias caused by the above-mentioned causes. The ECG may be the easiest method to determine if the heart muscle is affected in patients hospitalized after the earthquake and what negative consequences increased electrolytes may have on the heart.[2-4]

In this study, we aimed to determine the ECG findings in earthquake victims who were admitted to our hospital after the Kahramanmaraş earthquake.

METHODS

The study was carried out with the permission of Gazi Yaşargil Training and Research Hospital Clinical Researches Ethics Committee (Date: 04.08.2023, Decision No: 499). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In the first hours of the earthquake, only patients transferred from Diyarbakır province and its districts were accepted to our hospital. However, in the later hours of the earthquake, the injured people rescued from the rubble in the provinces of Kahramanmaraş, Adıyaman, Hatay, Şanlıurfa, and Gaziantep began to be referred to our hospital, and follow-up and treatment processes were initiated by the earthquake response committee.

We included all patients who applied to Diyarbakır Gazi Yaşargil Training and Research Hospital as earthquake victims in the study. We recorded patients' age, gender, time spent under the rubble, duration of hospitalization, needing for intensive care unit, duration of intensive care unit, laboratory parameters at the time of admission, clinical course. Laboratory parameters (ure, creatinin, potassium, creatinin phosphokinase (CPK), total calcium, phosphate, uric acid, white blood cell (WBC), hemoglobin, neutrophil, lymphocyte, platellet, C-reactive protein (CRP), albumin, pH and bicarbonate), ECG, 24-hour urine volumes, type of trauma (extremity, head, thorax, abdominal, spinal), penetrating injury, need for fasciotomy, need for amputation, presence of compartment syndrome, presence of crush syndrome, presence of acute kidney injury (AKI) and deceased patients were recorded. The total number of injured patients removed from the rubble after the earthquake and admitted to our hospital was 321. 182 of 321 patients were discharged from the emergency department after completing their treatment. A total of 139 patients were admitted to our hospital. Since the ECG recordings of 40 hospitalized patients were available, this number of patients was included in the study. ECG recordings were performed at a speed of 25 mm/s and an amplitude of 10 mm/mV using a Schiller AT 102 G2 12-lead/12-channel ECG machine. All ECGs were scanned at a resolution of 300 DPI and transferred to an electronic storage medium. The images were evaluated using the program "Adobe Photoshop CS2 Version 9.0" with a resolution of 1500 DPI and an accuracy of four milliseconds. Standard measurements such as heart rate (HR), P-wave duration, P-amplitude, PR interval, QRS complex, T-wave duration, T-amplitude, QT interval and QTc interval were performed for all ECGs and the ratios of Tp-e/QT and Tp-e/QTc were measured electrocardiographically. The duration of the P wave was assessed as the duration between the initial deflection and its return junction to the isoelectric baseline. QT interval was calculated as the duration between the onset of the QRS complex and the end of T wave in the isoelectric baseline. QTc was measured using Bazett's formula ($QTc=QT/\sqrt{RR}$). Tp-e interval was evaluated as the duration between the peak and the end of the T wave on isoelectric baseline. PR prolongation is defined as prolongation of the PR interval on an electrocardiogram (ECG) to more than 200 msec. An ST elevation is considered significant if the vertical

distance inside the ECG trace and the baseline at a point 0.04 seconds after the J-point is at least 0.1 mV (usually equivalent to 1 mm or 1 small square) in a limb lead or 0.2 mV (2 mm or 2 small squares) in a precordial lead. T-wave inversion is defined as a negative T-wave ≥1 mm deep in two or more adjacent leads, with the exception of leads aVR, III and V1. The patients were divided into groups, e.g. those who developed crush syndrome and those who required intensive care and those who did not, and were compared in terms of their clinical characteristics.

Statistical Analysis

Variables with normal distribution are presented as mean±standard deviation, and variables without normal distribution are presented as median (minimum-maximum). The p value obtained by comparing normally distributed numerical variables with the independent sample t test and the p value obtained by comparing non-normally distributed numerical variables with the Mann-Whitney U test are given. The chi-square test result p is given by giving the percentage rates of categorical variables and taking into account the expected value. The statistical significance level was accepted as $p<0.05$.

RESULTS

The demographic, clinical and ECG characteristics of the patients are shown in Table 1. The mean and median ages were 29.4 and 27 years, respectively. It was found that 60% of the patients (n=24) were female. The majority of patients (n=34, 85%) were adults. Regarding the type of trauma, extremity trauma was the most common type of trauma (77.5%, n=31 patients). The mean and median hours timing under the rubble were 17.6 hours and 7 hours, respectively. Crush syndrome developed in 45% of patients, while 25% developed acute renal failure. As expected, compartment syndrome was more common in patients with crush syndrome (66.7% vs 18.2%, p=0.002). The proportion of patients requiring dialysis treatment was 12.5% (n=5). The proportion of patients who received further treatment in the intensive care unit was 35% (n=14).

The clinical characteristics of the patients in terms of Crush syndrome are shown in Table 2. As expected, oligo-anuria was higher in patients with crush syndrome (5 vs 0, p=0.013). Regarding the type of trauma, although extremity trauma was found to be more common in patients with crush syndrome (88.9% vs 68.2%, p=0.118), no statistical significance was found. AKI developed in half of patients with crush syndrome (9 vs. 1, p=0.001), and dialysis treatment was required in 27.8% (5 vs. 0, p=0.013) of patients with crush syndrome. Urea levels were higher in patients with crush syndrome (60 mg/dl vs. 40 mg/dl, p=0.001), while no difference was observed for creatinine. Potassium levels were higher in patients with crush syndrome (4.8 mmol/l vs. 4 mmol/l, p=0.006). Uric acid was higher in patients with crush syndrome (5 mg/dl vs. 3.5 mg/dl, p=0.034). CRP was higher in patients with crush syndrome (117 IU/L vs. 36 IU/L, p=0.004). Albumin levels were lower in patients with crush syndrome (21 g/L vs. 31.3 g/L, p<0.001). HCO3 was lower in patients with crush syndrome (19.8 mmol/L vs. 23 mmol/L, p=0.046). Regarding ECG findings, the PR interval was longer (0.17 mm vs. 0.16, p=0.006 and prolonged PR patients' rate 57.1% vs 23.1%, p=0.036), the QRS distance was shorter (0.06 vs. 0.072, p=0.021) and the T wave was shorter (0.142 vs. 0.18, p=0.030) in patients with crush syndrome.

Table 1. Clinical characteristics of patients

Age, years	29.4+13.5 / 27 (8-66)
Gender, f/m (f%)	24/16 (60%)
Adult, y/n (yes%)	34/6 (85%)
Oligo-anuria, y/n (y%)	5/35 (12.5%)
Abdominal trauma, y/n (y%)	1/39 (2.5%)
Thoracic trauma, y/n (y%)	3/37 (7.5%)
Head trauma, y/n (y%)	3/37 (7.5%)
Extremity trauma, y/n (y%)	31/9 (77.5%)
Spinal trauma, y/n (y%)	3/37 (7.5%)
Penetrating trauma, y/n (y%)	12/28 (30%)
Crush syndrome, y/n (y%)	18/22 (45%)
Acute kidney injury, y/n (y%)	10 (25%)
Dialysis treatment, y/n (y%)	5/35 (12.5%)
Compartment syndrome, y/n (y%)	16/24 (40%)
Fasciotomy, y/n (y%)	10/30 (25%)
ICU admission, y/n (y%)	14/26 (35%)
Amputation, y/n (y%)	4/36 (10%)
Mortality, y/n (y%)	1/39 (2.5%)
Timing under the rubble, hours	17.6±37.7/7 (1-152)
Day of hospitalization	10.3±7.84/7 (2-34)
ICU, days	9.43±7.2/8 (2-28)
Ure, mg/dl	57±52/31 (15-200)
Creatinin, mg/dl	1.23±1.12/0.69 (0.48-4.68)
Potassium, mmol/L	4.4±5.2/4.2 (2.7-6.8)
CPK, U/L	36569±44602 / 21154 (165-190000)
Total calcium, mg/dl	8.1±1.1/8.2 (4.6-10)
Phosphate, mg/dl	3.5±1.5/3.2 (1.8-8.7)
Uric acid, mg/dl	4.3±2.24/3.6 (0.9-10.5)
WBC, $x10^3$/ml	15.7±6.9/14.1 (1.8-33.7)
Hemoglobin, mg/dl	14.1±3.24/13.9 (6.9-22.4)
Neutrophil, $x10^3$/ml	13±6.5/11.7 (1.5-3.1)
Lymphocyte, $x10^3$/ml	1.6±0.8/1.5 (0.2-4)
Platellet, $x10^3$/ml	260±94/247 (65-560)
CRP, IU/L	79±61 / 69 (2-224)
Albumin g/L	27.2±7.1/28 (11-38)
pH	7.37±0.09/7.38 (7.01-7.51)
$HC0_3$, mmol/L	21.7±4.7/22.8 (9-31)

a: Independent sample-t test, b: Pearson Chi-square test, c: Fisher's exact test, d: Mann Whitney-U test, ICU: Intensive care unit, CPK: Creatine phosphokinase, WBC: White blood cell, CRP: C-reactive protein

Table 2. According to crush syndrome patients' clinical characteristics

	Crush Syndrome		p
	No (n=22)	Yes (n=18)	
Age, years	27.5±9.4	31.8±17.3	0.344[a]
Gender, f/m (f%)	15/7 (68.2%)	9/9 (50%)	0.243[b]
Adult, y/n (yes%)	19/3 (86.4%)	15/3 (83.3)	0.565[c]
Timing under the rubble, hours	7 (1-144)	7 (5-152)	0.610[d]
Oligo-anuria, y/n (y%)	0/22 (0%)	5/13 (27.8%)	0.013[c]
Abdominal trauma, y/n (y%)	1/21 (4.5%)	0/18 (0%)	0.550[c]
Thoracic trauma, y/n (y%)	2/20 (1.7%)	1/17 (5.6%)	0.577[c]
Head trauma, y/n (y%)	2/20 (9.1%)	1/17 (5.6%)	0.577[c]
Extremity trauma, y/n (y%)	15/7 (68.2%)	16/20 (88.9%)	0.118[c]
Spinal trauma, y/n (y%)	3/19 (13.6%)	0/18 (0%)	0.156[c]
Penetrating trauma, y/n (y%)	7/15 (31.8%)	5/13 (27.8%)	0.781[b]
Acute kidney injury, y/n (y%)	1/21 (4.5%)	9/9 (50%)	0.001[b]
Dialysis treatment, y/n (y%)	0/22 (0%)	5/13 (27.8%)	0.013[c]
Compartment syndrome, y/n (y%)	4/18 (18.2%)	12/6 (66.7%)	0.002[b]
Fasciotomy, y/n (y%)	3/19 (13.6%)	7/11 (38.9%)	0.071[c]
Ure, mg/dL	28 (18-56)	60 (15-200)	0.001[d]
Creatinin, mg/dL	0.62 (0.48-1.18)	0.77 (0.5-4.63)	0.075[d]
Potassium, mmol/L	4±0.5	4.8±1.1	0.006[a]
CPK, U/L	4380 (165-84594)	41511 (1055-249203)	0.006[d]
Total calcium, mg/dl	8.8 (8-10)	7.5 (4.6-8.3)	<0.001[d]
Phosphate, mg/dl	3.1±0.5	4.1±2.1	0.060[a]
Uric acid, mg/dl	3.5±1.4	5±2.4	0.034[a]
WBC, $x10^3$/ml	14.8±5.4	16.7±8.4	0.391[a]
Hemoglobin, mg/dL	14±2.8	14.3±3.8	0.801[a]
Neutrophil, $x10^3$/ml	12.1±5.4	14.2±7.7	0.321[a]
Lymphocyte, $x10^3$/ml	1.8±0.9	1.4±0.6	0.108[a]
Platellet, $x10^3$/ml	279±97	236±87	0.155[a]
CRP, IU/L	36 (2-164)	117 (10-224)	0.004[d]
Albumin g/L	31.3 (26-38)	21 (11-33)	<0.001[d]
pH	7.39±0.05	7.34±0.13	0.072[a]
HC03, mmol/L	23±3.6	19.8±5.7	0.046[a]
ECG, pulse rate	90±15	96±19	0.201[a]
QT, ms	0.35±0.027	0.34±0.037	0.596[a]
QTc, ms	0.420±0.034	0.428±0.021	0.540[a]
P amplitute, mV	0.1 (0.06-0.94)	0.1 (0.06-0.15)	0.878[d]
P wave, ms	0.08 (0.06-0.12)	0.08 (0.06-0.12)	0.146[d]
PR, sn	0.16 (0.12-0.30)	0.17 (0.1-0.3)	0.006[d]
QRS, ms	0.072 (0.03-0.48)	0.06 (0.04-0.10)	0.021[d]
T amplitute, mV	0.2 (0.08-0.9)	0.12 (0.08-0.3)	0.266[d]
T wave, ms	0.18±0.04	0.142±0.05	0.030[a]
Tpe, ms	0.099±0.024	0.098±0.023	0.962[a]
Tpe/QT	0.28±0.07	0.28±0.06	0.836[a]
Tpe/QTc	0.24±0.06	0.23±0.06	0.988[a]
ST elevation, y/n (y%)	11/11 (50%)	7/11 (38.9%)	0.482[b]
T wave inversion, y/n (y%)	7/15 (31.88%)	4/14 (22.2%)	0.337[c]
PR prolongation, y/n (y%)	8/14 (36.4%)	6/12 (33.3%)	0.842[b]

a: Independent sample-t test b: Pearson Chi-square test c: Fisher's exact test d: Mann Whitney-U test, ICU: Intensive care unit CPK: Creatine Phosphokinase WBC: White blood cell CRP: C-reactive protein

The clinical characteristics of the patients with and without the need for intensive care unit are shown in Table 3.

Table 3. The clinical characteristics of the patients with and without the need for intensive care unit

	ICU admission		p
	No (n=26)	Yes (n=14)	
Age, years	29.9±12.3	28.4±15.9	0.737[a]
Gender, f/m (f%)	17/9 (65.4%)	7/7 (50%)	0.343[b]
Adult, y/n (yes%)	23/3 (88.5%)	11/3 (78.6)	0.346[c]
Timing under the rubble, hours	7 (1-152)	7 (6-144)	0.808[d]
Oligo-anuria, y/n (y%)	2/24 (7.7%)	3/11 (21.4%)	0.222[c]
Abdominal trauma, y/n (y%)	1/25 (3.8%)	0/14 (0%)	0.650[c]
Thoracic trauma, y/n (y%)	1/25 (3.8%)	2/12 (14.3%)	0.276[c]
Head trauma, y/n (y%)	2/24 (7.7%)	1/13 (7.1%)	0.724[c]
Extremity trauma, y/n (y%)	17/9 (65.4%)	14/0 (100%)	0.011[c]
Spinal trauma, y/n (y%)	2/24 (7.7%)	1/13 (7.1%)	0.724[c]
Penetrating trauma, y/n (y%)	9/17 (34.6%)	3/11 (21.4%)	0.311[c]
Crush syndrome, y/n (y%)	8/18 (30.8%)	10/4 (71.4%)	0.014[b]
Acute kidney injury, y/n (y%)	4/22 (15.4%)	6/8 (42.9%)	0.065[c]
Dialysis treatment, y/n (y%)	2/24 (7.7%)	3/11 (21.4%)	0.222[c]
Compartment syndrome, y/n (y%)	5/21 (19.2%)	11/3 (78.6%)	<0.001[b]
Fasciotomy, y/n (y%)	4/22 (15.4%)	6/8 (42.9%)	0.065[c]
Ure, mg/dL	29.5 (15-122)	56 (18-200)	0.023[d]
Creatinin, mg/dL	0.67 (0.48-3.9)	0.67 (0.6-4.63)	0.305[d]
Potassium, mmol/L	4.1±0.5	4.6±1.2	0.047[a]
CPK, U/L	7957 (165-190000)	24679 (470-249203)	0.200[d]
Total calcium, mg/dl	8.7 (5.8-10)	7.9 (4.6-9.1)	0.013[d]
Phosphate, mg/dl	3.1±0.8	4.4±2.1	0.060[a]
Uric acid, mg/dl	3.7 (1.7-10.5)	3.9 (0.9-8.4)	0.738[d]
WBC, $x10^3$/ml	15.2±5.6	16.6±8.9	0.559[a]
Hemoglobin, mg/dl	14.1±2.3	14.2±4.6	0.963[a]
Neutrophil, $x10^3$/ml	12.6±5.5	13.9±8.3	0.565[a]
Lymphocyte, $x10^3$/ml	1.7±0.9	1.4±0.6	0.296[a]
Platellet, $x10^3$/ml	271±98	238±86	0.296[a]
CRP, IU/L	50 (2-184)	122 (2-224)	0.025[d]
Albumin g/L	30.5 (13-38)	23 (11-32)	0.001[d]
pH	7.38 (7.27-7.51)	7.39 (7.01-7.50)	0.856[d]
HC03, mmol/L	22.6±3.9	20.1±5.8	0.118[a]
Heart pulse rate, per minute	86±13	105±16	<0.001[a]
QT, ms	0.35±0.027	0.33±0.034	0.021[a]
QTc, ms	0.420±0.029	0.432±0.027	0.181[a]
P amplitute, mV	0.1 (0.06-0.94)	0.1 (0.06-0.20)	0.878[d]
P wave, ms	0.08 (0.06-0.12)	0.08 (0.06-0.12)	0.146[d]
PR, ms	0.14 (0.12-0.30)	0.2 (0.1-0.3)	0.006[d]
QRS, ms	0.077 (0.04-0.48)	0.05 (0.03-0.09)	0.021[d]
T amplitute, mV	0.15 (0.08-0.9)	0.15 (0.08-0.5)	0.266[d]
T wave, ms	0.168±0.04	0.143±0.06	0.166[a]
Tpe, ms	0.1 (0.04-0.14)	0.1 (0.06-0.13)	0.946[d]
Tpe/QT	0.28±0.07	0.29±0.05	0.619[a]
Tpe/QTc	0.24±0.06	0.23±0.05	0.602[a]
ST elevation, y/n (y%)	14/11 (56%)	4/7 (36.4%)	0.278[b]
T wave inversion, y/n (y%)	7/18 (28%)	4/7 (36.4%)	0.449[c]
PR prolongation, y/n (y%)	6/20 (23.1%)	8/6 (57.1%)	0.036[c]

a: Independent sample-t test b: Pearson Chi-square test c: Fisher's exact test d: Mann Whitney-U test, ICU: Intensive care unit CPK: Creatine Phosphokinase WBC: White blood cell CRP: C-reactive protein

There were no differences between the groups in terms of age, sex, adult/child, time under debris and presence of oligo-anuria. All patients (n=14) admitted to the ICU (100% vs. 65.4%, p=0.011) had extremity trauma. Crush syndrome was more common in patients treated in the ICU (71.4% vs. 30.8%, p=0.014). Compartment syndrome was more common in patients treated in the intensive care unit (78.6% vs. 19.2%, p<0.001). Urea levels were higher in patients treated in the ICU (56 mg/dl vs. 29.5 mg/dl, p=0.023). Potassium levels were higher in ICU patients (4.6 mmol/l vs 4.1 mmol/l, p=0.047). Calcium levels were lower in ICU patients (7.9 mg/dl vs. 8.7 mg/dl, p=0.013). CRP was higher in ICU patients (1222 IU/L vs. 50 IU/L, p=0.025). Albumin levels were lower in ICU patients (23 g/L vs. 30.5 g/L, p=0.001).

In terms of ECG characteristics, heart rate was higher in ICU-treated patients (105/min vs 86/min, p<0.001), PR interval was longer in ICU-treated patients (0.2 s vs 0.14 s; proportion of patients with long PR was 57.1% vs 23.1% p=0.006), QRS complex was shorter in ICU-treated patients (0.05 mm vs 0.077 mm, p=0.021). QT interval was shorter in patients who admitted to intensive care unit (0.33 vs 0.35, p=0.021). In patients with crush syndrome, PR interval was longer (0.17 vs 0.16, p=0.006), QRS width was shorter (0.006 vs 0.072, p=0.021). In addition, the T-amplitude in the ECG was found to be higher in those who developed AKI compared to those who did not (0.20 vs. 0.10, p=0.018). Again, the T-amplitude was higher in those who required dialysis treatment (0.20 vs. 0.10, p=0.009).

DISCUSSION

In this study, we showed that there were some ECG changes in the patients admitted to our hospital from the victims of the Kahramanmaraş earthquake. We showed that the PR interval was longer and the QRS width was shorter in patients who developed crush syndrome and required further treatment in the intensive care unit. We also showed that the heart rate was higher in patients admitted to the ICU and the T wave was narrower in patients who developed crush syndrome. We were able to show that the T amplitude was longer in patients who developed AKI and in patients who required dialysis treatment.

ECG changes seen in people trapped under rubble may be the result of traumatic rhabdomyolysis, which develops as a result of prolonged pressure on the muscles, tissue hypoxemia, which may develop as a result of fluid and nutrient deprivation, an increased calcium load that develops in the muscle cell after reperfusion following the person's rescue from the rubble, released oxygen radicals and potassium, adverse effects of increased sympathetic activity, an increase in antidiuretic hormone, and cardiac effects of an active renin angiotensin aldosterone system (RAAS).[5,6] Experimental studies have shown that there are numerous ECG changes following decompression that are due to both the direct effect of the trauma on the myocardium and the prolonged muscle injury.[7-9] These changes include increased heart rate, ST segment elevation, ST segment depression, prolonged PR interval, T wave changes, arrhythmias, abnormal Q wave, QT prolongation, wide QRS wave.[7-9]

In people trapped under rubble in earthquakes, adverse effects on the heart may occur as a result of hypovolemia, increased sympathetic activity, many electrolytes released into the blood after muscle injury, free radicals, and triggering of cytokines and various hormonal pathways as a result of immune system activation. The negative effects of the earthquake on the heart and the increase in cardiovascular events persist not only at the time of the earthquake, but also in the months that follow. The number of sudden cardiac deaths in earthquake victims has been shown to increase in earthquake victims.[10] When muscle contusion develops in earthquake victims, many unfavorable clinical outcomes such as fasciotomy, amputation, AKI, and the need for renal replacement therapy occur in these individuals. Therefore, these individuals may need to be hospitalized and some of them may require further treatment in the intensive care unit to monitor these clinical pictures. After the Kahramanmaraş earthquake, many earthquake victims were hospitalized and continued to be treated in the ICU depending on their clinical condition.[11-13] In the study conducted by Sarı et al.[11] on the victims of the Maraş earthquake, 38.3% of hospitalized patients were hospitalized, 17.4% of these patients were admitted to the ICU, 16.9% of hospitalized patients required hemodialysis, and 8.3% of patients died. In a study conducted by Koyuncu et al.[12] on Kahramanmaraş Earthquake victims admitted to Kayseri City Hospital, it was found that 7.4% of patients developed crush syndrome, 2.73% required AKI, 2.23% required hemodialysis, 4% required intensive care, and 1.29% died. In a study of pediatric victims of the Kahramanmaraş Earthquake conducted by Döven et al.[13] it was found that 16% were hospitalized and followed up, 9.1% developed crush syndrome, 1.85% required intensive care, and 1.54% required hemodialysis treatment. There were no deaths in this series. A significant proportion of deaths among earthquake victims can be attributed to cardiovascular causes.

ECG, a simple method for follow-up of hospitalized patients, can be used as a predictive tool for cardiovascular assessment of patients and mortality. Erdem et al.[14] demonstrated that a score obtained from the ECG of ICU patients has the same sensitivity and specificity as the APACHE-II score for non-cardiac mortality. George et al.[15] showed that prolonged QT time was associated with adverse clinical outcomes in adult ICU patients, and Ozdemir et al.[16] showed that the Tpe/QT ratio may be an effective tool for predicting mortality in pediatric ICU patients. In our study, we found that the heart rate was higher, the PR interval was shorter and the QRS was shorter in earthquake victims who were treated in the intensive care unit.

As a result of muscle contusion, patients develop hypocalcemia and hyperkalemia. Pathological ECG findings may be observed due to these electrolyte disturbances. Hypocalcemia may be severe in the first few days after muscle contusion due to the high accumulation of calcium in the muscle cells. In the following days, calcium levels are expected to return to normal due to release from the muscle cells into the plasma. Hypocalcemia prolongs phase 2 of the action potential depending on the rate of change in serum calcium concentration and myocyte calcium channel function.

Prolongation of the QT interval is associated with premature depolarizations and triggered arrhythmias. Although electrocardiographic conduction disturbances are common, severe arrhythmias due to hypocalcemia such as heart block and ventricular arrhythmias are rare. Hyperkalemia may be accompanied by various changes in the electrocardiogram (ECG). A shortened QT interval and high T waves are usually the first findings. As hyperkalemia worsens, the PR interval and QRS duration become progressively longer, the P wave may disappear, and eventually the QRS broadens to a sinus wave pattern. In the complete absence of electrical activity, ventricular arrest occurs with a flat line on the ECG.[17-19] In our study, although total calcium levels were found to be significantly lower in patients who developed crush syndrome and were followed up in the ICU, there was no difference between the groups in terms of QTc. This is probably due to the fact that albumin levels were also significantly lower and ionized calcium levels were similar in patients who developed crush syndrome and continued in the ICU. It is likely that the total calcium values in our study were not adjusted for albumin. The longer PR interval and narrower T wave could be due to hyperkalemia, and we may not have seen prolongation of the QT interval due to hyperkalemia.

Limitations

The limitations of our study are as follows. First, the number of cases was very small. Second, the association between ECG and adverse clinical outcomes could not be investigated. Third, due to the fact that only one ECG was evaluated at the time of hospitalization, it was not possible to detect ECG abnormalities that may develop over time. Finally, the study did not provide information on the physiopathologic process between ECG abnormalities and clinical outcomes in earthquake victims.

CONCLUSION

In this study, we demonstrated some possible ECG changes such as PR prolongation and narrow QRS in earthquake victims admitted to our hospital. ECG can be used as a simple but predictive tool to monitor cardiovascular outcomes in earthquake victims. Further studies in which the ECG is monitored in a larger group of patients and throughout the process could provide more information on this topic.

Hypocalcemia prolongs phase 2 of the action potential, with effects depending on the rate of change in serum calcium concentration and myocyte calcium channel function. Prolongation of the QT interval is associated with early afterdepolarizations and triggered arrhythmias. Although electrocardiographic conduction abnormalities are common, severe arrhythmias due to hypocalcemia, such as heart block and ventricular arrhythmias, are rare. Hyperkalemia can be accompanied by a variety of changes in the electrocardiogram (ECG). High T waves with a shortened QT interval are usually the first finding. As hyperkalemia worsens, the PR interval and QRS duration become progressively longer, the P wave may disappear, and eventually the QRS broadens to a sinus wave pattern. A ventricular arrest with a straight line on the ECG occurs in the complete absence of electrical activity.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Gazi Yaşargil Training and Research Hospital Clinical Researches Ethics Committee (Date: 04.08.2023, Decision No: 499).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1454031
J Health Sci Med. 2024;7(3):278-283

The relationship between the need for oxygen concentrator after discharge in COVID-19 patients and mortality

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Cite this article as: Doğru S, Uyar M, Aytaç S, Ovayolu Ö. The relationship between the need for oxygen concentrator after discharge in COVID-19 patients and mortality. *J Health Sci Med.* 2024;7(3):278-283.

Received: 16.03.2024 ◆ **Accepted**: 18.04.2024 ◆ **Published**: 27.05.2024

ABSTRACT

Aims: The COVID-19 pandemic has severely burdened healthcare systems worldwide due to the rapid rise in cases, often resulting in respiratory distress requiring oxygen therapy. However, research on the availability and long-term usage of oxygen concentrators upon discharge is limited. This study aimed to identify factors associated with the need for oxygen concentrators in discharged COVID-19 patients, as well as device acquisition and mortality rates.

Methods: This study, conducted at a single center, comprised retrospective and prospective phases. Data were gathered from hospitalized COVID-19 patients, with follow-up conducted one year later for those prescribed oxygen concentrators at discharge. Sociodemographic and clinical variables were recorded, and statistical analyses were conducted to determine factors associated with oxygen concentrator need and duration of use.

Results: Among 229 patients, 15.7% required oxygen concentrators at discharge. Factors associated with this need included older age, asthma, bilateral lung lesions, and the severity of lesions detected on thoracic computed tomography scans. Patients with corticosteroid use and hypertension required oxygen concentrators for over three months. Economic limitations impeded the acquisition of devices for 22.2% of patients who were prescribed them. Two to three months post-discharge, 72.2% of patients still used oxygen concentrators. Mortality analysis showed a 16.6% fatality rate among oxygen concentrator prescribed patients within one year, with shorter survival observed in those unable to obtain the device.

Conclusion: This study highlights the significance of assessing factors impacting oxygen concentrator requirement in COVID-19 patients and their long-term prognosis. These findings should inform healthcare providers and policymakers in pandemic preparedness efforts, emphasizing tailored treatment approaches based on individual patient characteristics. Ensuring device accessibility and regular patient follow-up are crucial for optimizing healthcare delivery during similar crises.

Keywords: Oxygen concentrator, mortality rates, pandemic preparedness, COVID-19, coronavirus disease

INTRODUCTION

The COVID-19 pandemic has caused a significant global health crisis.[1] The pandemic has strained global healthcare systems, stretching hospital resources beyond capacity due to a rapid increase in cases, particularly in meeting treatment needs such as beds, medications, and oxygen.[2]

The deadly impact of COVID-19 often results from lung parenchyma and airways involvement.[3] Lung involvement in COVID-19 can lead to acute respiratory distress syndrome (ARDS) in the early stages and varying degrees of fibrosis in the chronic stages. These conditions may result in respiratory failure and hypoxia, requiring oxygen support therapy. As approximately 15% of hospitalized patients need oxygen, clinically stable patients with ongoing oxygen requirements are discharged with an oxygen concentrator.[4,5] While many studies explore factors associated with the need for oxygen concentrators, there's a limited number of studies assessing the availability of the device and its long-term usage.[4,5]

This study aimed to identify factors associated with the necessity for oxygen concentrators upon discharge of COVID-19 patients, alongside investigating device acquisition and mortality rates.

METHODS

Ethics

The study adhered to the Helsinki Declaration and received approval from the Gaziantep University Clinical Researches Ethics Committee (Date: 18.01.2023, Decision No: 2022/454).

Study Population

This study included patients diagnosed with COVID-19 pneumonia and treated at Gaziantep University's Chest Diseases Clinic. A sample size of 102 was determined using power analysis (α=0.05; 1-β=0.80) with G Power 3.9.1

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software. Eligible participants were adults aged 18 and above with moderate to severe COVID-19 confirmed via real-time reverse transcriptase polymerase chain reaction (RT-PCR) from throat swab samples. Patients with prior oxygen concentrator use were excluded from the study.

Study Design

This single-center study involves retrospective and prospective phases. In the retrospective phase, data were gathered from the Hospital Information System on COVID-19 patients hospitalized between 01.03.2019 and 30.12.2022. Patient forms were used to record this data. During the prospective phase, discharged patients prescribed with oxygen concentrators were contacted via telephone one year later to assess their usage. Mortality status within the past year was obtained from the Hospital Information System.

Variables

Patients' sociodemographic and clinical characteristics, including age, gender, length of hospital stay, oxygen requirement during hospitalization, COVID-19 severity, presence and number of comorbidities (asthma, COPD, bronchiectasis, Type 2 Diabetes Mellitus, hypertension), unilateral/bilateral lesions on posteroanterior chest X-ray, thoracic computed tomography (CT) involvement score, were documented. Additionally, the use of corticosteroids, antibiotics, low molecular weight heparin, interleukin-6 blocker, and route of oxygen delivery during hospitalization were recorded. Upon discharge, the prescription of oxygen concentrators was noted. Follow-up after one year included recording the duration of oxygen concentrator usage, reasons for non-usage if applicable, and mortality status.

Severity of COVID-19 disease: During hospitalization, patients presenting pneumonia symptoms with room air oxygen saturation (SpO_2)≥90% were categorized as having "moderate" COVID-19 disease, while those with SpO_2<90% were classified as having "severe" disease.[6]

The thoracic computed tomography (CT) involvement score was determined by assessing findings consistent with COVID-19 pneumonia (GE64R, Japan). Each lobe's pathological findings were scored as follows: 0 for no involvement, 1 for ≤5% involvement, 2 for involvement between 5% and 25%, 3 for involvement between 25% and 50%, 4 for involvement between 50% and 75%, and 5 for involvement >75%.[7]

Indications for prescribing oxygen concentrators upon discharge were as follows: Patients treated at the Chest Diseases Clinic, hospitalized for at least 24 hours, without dyspnea, cough, sputum, or fever, and lacking hemodynamic instability (systolic blood pressure <90 mmHg, heart rate >120 bpm), were categorized as "patients requiring oxygen concentrator upon discharge-Group I" if their room air SpO_2 was ≤88%. Those with SpO_2>88% were classified as "patients not requiring oxygen concentrator upon discharge-Group II".[4]

Statistical Analysis

Data analysis was conducted using IBM SPSS Statistics (version 22.0, IBM Corp., Armonk, NY, USA). Descriptive statistics, including frequencies, percentages, means, and standard deviations, were employed. The Shapiro-Wilk test assessed the normality of continuous variables. Student's t-test was used to examine differences in means between groups, while the Mann-Whitney U test assessed differences in medians. Nominal variables were evaluated using Pearson's chi-square test or Fisher's exact test. Variables showing significance through basic statistical methods underwent further evaluation using logistic regression. Mortality rate within one year was analyzed using the Kaplan-Meier method. A p-value <0.05 was considered statistically significant.

RESULTS

The study included 229 patients with a mean age of 62.9±15.4 years, of whom 125 (54.6%) were male. The median hospitalization duration was 6.1 days. Oxygen was required by 192 patients (83.8%) during hospitalization, with 114 (51.6%) classified as having moderate and 107 (48.4%) as having severe COVID-19 infection. Eight patients lacked sufficient information for disease severity assessment. Some demographic and clinical characteristics of patients shown in Table 1.

Table 1. Some demographics and clinical characteristics of patients

Variables	n, %
Age (mean±SD)	62.9±15.4
Gender	
Male	125,54.6%
Female	104,45.4%
Total days of hospitalization (median/min-max)	6.1/1-25
Oxygen requirement during hospitalization	
Yes	192,83.8%
No	37,16.2%
COVID-19 case severity	
Moderate	114,51.6%
Severe	107,48.4%
Number of comorbidities	167,72.9%
Presence of comorbidities	
Asthma	42,18.3%
COPD	13,5.7%
Bronchiectasis	9,3.9%
Diabetes mellitus	77,33.6%
Hypertension	64,27.9%
Lesion on chest X-ray	
Unilateral	24,10.5%
Bilateral	205,89.5%
Lesion severity on thoracic CT (mean±SD)	11.2,±6.6
Treatments used during hospitalization	
Corticosteroid	97,42.4%
Antibiotic	222,96.9%
LMWH	145,63.3%
IL6 blocker	11,4.8%
Oxygen support	
Nasal oxygen	162,84.4%
Non-invasive mechanical ventilation	30,15.6%
Discharge status	
Discharged with recovery	207,90.4%
Transferred to intensive care	20,8.7%
Exitus	2,0.9%
Oxygen concentrator need at discharge	
Yes	36,15.7%
No	194,84.3%
Acquisition of oxygen concentrator	
Yes	18,50%
No	8,22.2%
Unreachable	10,27.8%

SD: Standart deviation, Min: Minimum, Max: Maximum, COPD: Chronic obstructive pulmonary disease, CT: Computed tomography, LMWH: Low molecular weight heparin

The comparison of the characteristics of Group I and Group II is shown in Table 2. In Group I (n=36, 16.1%), patients had an average age of 68.3±12.5 years, while in Group II (n=193, 83.9%), the average age was 61.9±15.7 years (p=0.01). Although Group I had more severe COVID-19 cases, comorbidities such as asthma, bilateral lesions on PA chest X-ray, and extensive thoracic CT lesions compared to Group II, logistic regression analysis did not identify these variables as independent risk factors for determining the need for oxygen concentrator upon discharge.

Table 2. A comparison between patients requiring oxygen concentrator upon discharge and those not

Variables	Patients Requiring Oxygen Concentrator (n=36), n (%)	Patients Not Requiring Oxygen Concentrator (n=193), n (%)	p value
Age (mean±SD)	68.3±12.5	61.9±15.7	0.01
Gender			0.52
Male	20 (55.6%)	105 (54.4%)	
Female	16 (44.4%)	88 (45.6%)	
Total days hospitalized (median/min-max)	8 (2-23)	6 (1-25)	0.12
Oxygen requirement at admission			0.01
Yes	35 (97.2%)	157 (81.3%)	
No	1 (2.8%)	36 (18.7%)	
Severity of COVID-19			0.01
Moderate	11 (31.4%)	103 (55.4%)	
Severe	24 (68.6%)	83 (44.6%)	
Presence of comorbidities	29 (80.6%)	138 (71.5%)	0.94
Asthma	12 (33.3%)	30 (15.5%)	0.01
COPD	0 (0%)	13 (6.7%)	0.23
Bronchiectasis	2 (5.6%)	7 (3.6%)	0.63
Diabetes mellitus	12 (33.3%)	65 (33.7%)	0.56
Hypertension	10 (4.27.8%)	54 (28.0%)	0.57
Lesion on chest X-ray			0.03
Unilateral	0 (0.0%)	24 (12.4%)	
Bilateral	36 (100%)	170 (87.6%)	
Lesion severity on thorax CT (mean±SD)	13.7±7.7	10.6±6.2	0.03
Treatments during hospitalization			
Corticosteroid	19 (52.8%)	78 (40.4%)	0.19
Antibiotic	34 (94.4%)	188 (97.4%)	0.30
LMWH	19 (52.8%)	126 (65.3%)	0.18
IL6 blocker	4 (11.1%)	7 (3.6%)	0.07
Nasal oxygen	29 (82.9%)	133 (84.7%)	0.79
NIMV	6 (17.1%)	24 (15.3%)	
Outcome one year after prescription of oxygen concentrator			0.65
Alive	30 (80%)	150 (77.7%)	
Exitus	6 (20%)	43 (22.3%)	

SD: Standart deviation, Min: Minimum, Max: Maximum, COPD: Chronic obstructive pulmonary disease, CT: Computed tomography, LMWH: Low molecular weight Heparin, IL-6: Interleukin-6, NIMV: Non-invasive mechanical ventilation

Oxygen Concentrator Prescribed Patients' Characteristics

Out of 36 patients prescribed oxygen concentrators, 50% obtained the device, 22.2% did not use it due to economic reasons, and 27.8% were unreachable for evaluation at the end of the first year. Among those who obtained the device, 16.6% used it for one month, 11.1% for two to three months, 16.6% for four to six months, and 55.5% for seven to twelve months.

The comparisons between patients using the device for less than three months and those using it for longer, as shown in Table 3, did not reveal statistically significant differences in most characteristics. However, corticosteroid use and hypertension during hospitalization were significantly higher in patients using the device for less than three months compared to those using it for more than three months (p=0.03, p=0.01 respectively).

When comparing oxygen concentrator usage durations (less than one month vs. one month and more, less than four months vs. four months and more, less than six months vs. six months and more) with various patient characteristics, including age, gender, total length of hospital stay, oxygen requirement during hospitalization, severity of COVID-19 cases, number of comorbidities, presence of asthma, COPD, bronchiectasis, diabetes mellitus, hypertension, unilateral/bilateral lesions on PA chest X-ray, lesion density on thoracic CT, use of corticosteroids, antibiotics, LMWH, and IL-6 blocker, no statistically significant difference was found (p>0.05).

Mortality Analysis of Patients Prescribed With Oxygen Concentrators

Among 36 patients discharged with oxygen concentrators, the one-month mortality rate was 0%, three-month mortality rate was 2.7%, and one-year mortality rate was 16.6%, with an average one-year survival time of 11.2 months. Six patients died after one year; among them, two were unreachable, and four were unable to obtain the oxygen concentrator. Excluding the unreachable patients, the average one-year survival time was 17.7 months for those who couldn't obtain the device and 22.3 months for those who obtained it, as shown in Figure.

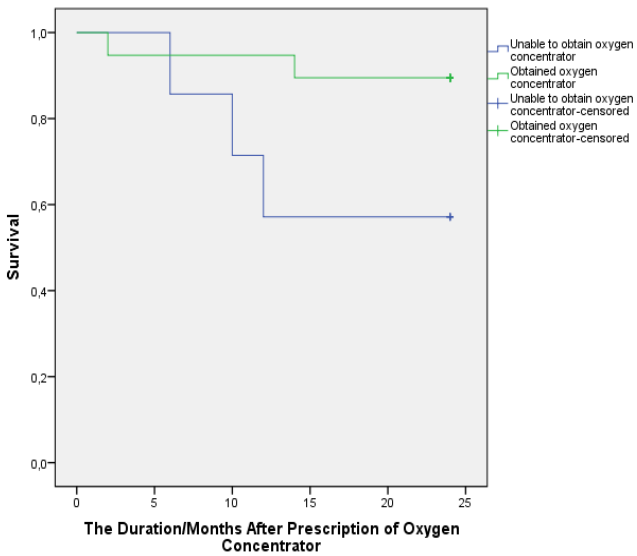

Figure. One-year mortality rates of patients using and not using oxygen concentrator

Table 3. Comparison of characteristics between patients who used oxygen concentrator for more than three months and less

Variables		Duration of oxygen concentrator usage			
		Usage of less than three months, n%	Usage of more than three months, n%	Total	p value
Age (mean±SD)		67.2±12.6	66.38±14.0		0.91
					0.27
Gender	Female	0 0%	4 22.2%	4 22.2%	
	Male	5 27.8%	9 50.0%	14 77.8%	
Total days of hospitalization median/min-max		8/3-18	9/4-13		0.71
Presence of oxygen requirement at admission		5 27.8%	13 72.2%	18 100%	Constant
Severity of COVID-19 case					0.65
	Moderate	1 5.6%	2 11.1%	3 16.7%	
	Severe	4 22.2%	11 61.1%	15 83.3%	
Comorbidities					0.70
	No	1 5.6%	3 16.7%	4 22.2%	
	Yes	4 22.2%	10 55.6%	14 77.8%	
Number of comorbidities		1.8±0.8	1.8±1.2		0.94
Asthma					0.24
	No	5 27.8%	8 44.4%	13 72.2%	
	Yes	0 0.0%	5 27.8%	5 27.8%	
Chronic obstructive pulmonary disease					Constant
	No	5 27.8%	13 72.2%	18 100%	
	Yes	0	0	0	
Bronchiectasis					0.86
	No	5 27.8%	11 61.1%	16 89.9%	
	Yes	0 0.0%	2 11.1%	2 11.1%	
Diabetes mellitus					0.58
	No	3 16.7%	10 55.6%	13%	
	Yes	2 11.1%	3 16.7%	5 27.8%	
Hypertension					0.01
	No	2 11.1%	12 66.7%	14 77.8%	
	Yes	3 16.7%	1 5.6%	4 22.2%	
Lesion on chest X-ray					
	Unilateral	0	0	0	Constant
	Bilateral	5 27.8%	13 72.2%	18 100%	
Severity of lesion on chest CT (mean±SD)		16.4±8.9	11.4±5.8		0.18
Treatments used during hospitalization					
Corticosteroid					0.03
	No	5 27.8%	5 27.8%	10 55.6%	
	Yes	0 0.0%	8 44.4%	8 44.4%	
Antibiotic					0.72
	No	0 0.0%	1 5.6%	1 5.6%	
	Yes	5 27.8%	12 66.7%	17 94.4%	
Low molecular weight heparin					0.32
	No	1 5.6%	6 33.3%	7 38.9%	
	Yes	4 22.2%	7 38.9%	11 61.1%	
IL-6 blocker					0.65
	No	4 22.2%	11 61.1%	15 83.3%	
	Yes	1 5.6%	2 11.1%	3 16.7%	

SD: Standart deviation, Min: Minimum, Max: Maximum, CT: Computed tomography, IL-6: Interleukin-6

DISCUSSION

This study found that older age, prior oxygen requirements, asthma, bilateral lung lesions, and severity of lesions on thoracic CT scans were associated with a higher need for oxygen concentrators at discharge. Patients using corticosteroids and those with hypertension required oxygen concentrators for over three months. Patients who were unable to purchase oxygen concentrators due to economic constraints experienced a higher mortality rate.

The observed need for oxygen concentrators upon discharge (15.7%) matched rates in other studies (13%-23%).[8] Obesity and African descent were linked to increased device necessity.[4] Individuals aged 50 and older with three or more comorbidities were 3.4 times more likely to need oxygen.[9]

In this study, patients needing oxygen concentrators were older compared to those not requiring the device. Similarly, Ray et al.[9] found higher oxygen requirements in patients over 60 years old compared to those under 50 years old. This suggests age as a determinant factor in oxygen requirements, emphasizing the need for age-specific treatment strategies.

Consistent with previous findings, showed no significant gender difference in oxygen requirement.[9] Diabetes mellitus (DM) remains consistently linked to COVID-19-related oxygen needs, underscoring the need for careful monitoring of discharged DM patients,[3,9,10] While previous studies often cite COPD among oxygen concentrator users, we observed a higher requirement in asthma patients.[11] However, our study's exclusion of COPD patients initially using concentrators may have inflated the proportion of asthma patients, contributing to this disparity.

The present study confirmed that patients with higher lesion density required more oxygen support initially. Literature suggests higher lesion density on thoracic CT scans at diagnosis correlates with increased oxygen requirement, while long-term requirements decrease as lesion density declines.[12,13] However, lesion density did not differ significantly between patients using oxygen concentrators for over three months and those using them for a shorter duration. This implies that while lesion density may predict short-term oxygen needs, its predictive value for long-term device requirement is limited. Thus, lesion density should be evaluated dynamically in early pandemic oxygen support decisions.

In this study, 22.2% of patients couldn't get oxygen concentrators due to economic issues, a new finding. Economic factors strongly affect healthcare access. Implementing economic support mechanisms could boost treatment adherence and enhance health outcomes.

Literature presents conflicting findings on oxygen concentrator need post-discharge. While one study showed a 38% usage rate one month post-discharge[14] another found only 6.5% requiring home oxygen support within two months. In our study, 72.2% still used the device two to three months post-discharge. Patient accessibility during follow-up may influence usage rates.[15]

In Kaul et al.'s[4] study, 32% of patients still required oxygen concentrators at the end of the sixth month, whereas in our study, it was 55.5%. Regular monitoring and treatment in Kaul et al.'s[4] study may have reduced the need for oxygen concentrators. Regular monitoring may have influenced outcomes.

Serrano et al.[16] found 12.4% needing concentrators at one year, while our study reported 27.7%. Differences in patient characteristics and methods may explain the variance.

In literature, patients with low saturation during hospitalization in the first three months, those in intensive care, and those with pre-existing lung disease have a 40% higher need for oxygen concentrators.[9] However, in our study, corticosteroid use and hypertension were associated with prolonged usage, suggesting their impact warrants further investigation.

In this study, the 30-day mortality rate was 0%, while the one-year mortality rate among patients prescribed with oxygen concentrators was 16.6%. Terp et al.[17] reported a 30-day mortality rate of 1.4% for patients discharged with oxygen concentrators, and Banerjee et al.[18] reported a 30-day mortality rate of 1.3%. However, these studies did not specify whether mortality was attributed to COVID-19, and the predominance of patients followed up in the emergency department may have influenced the results.

In current study, patients unable to obtain oxygen concentrators experienced shorter survival times. Implementing specialized follow-up programs and improving device accessibility are crucial. Incorporating patients' relatives' phone numbers into hospital systems may alleviate follow-up challenges.

Limitations

The main limitations include the small sample size, although it's comparable to similar studies. Lack of data on patients' COVID-19 vaccination status may have impacted outcomes. Some patients couldn't be reached during the one-year follow-up, potentially introducing bias. We didn't investigate the duration of device daily usage and compliance, which is another limitation.

CONCLUSION

This study highlights factors influencing oxygen concentrator need in COVID-19 patients and their status one year later, including age, oxygen requirement during hospitalization, disease severity, comorbidities like asthma, HT, and thoracic CT findings. Additionally, it is crucial to note economic barriers preventing the acquisition of the device. These insights can inform personalized treatment strategies for future pandemics.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Gaziantep University Clinical Researches Ethics Committee (Date: 18.01.2023, Decision No: 2022/454).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
The authors declared that this study has received no financial support.

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Acknowledgement
The authors are grateful to the anonymous reviewers for their comments, which have helped to improve the paper.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1461031
J Health Sci Med. 2024;7(3):284-289

Comparison of ultrasonographic parameters in the diagnosis of carpal tunnel syndrome in pregnancy

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Cite this article as: Bayraktarlı RY, Şahin F, Işın K. Comparison of ultrasonographic parameters in the diagnosis of carpal tunnel syndrome in pregnancy. *J Health Sci Med.* 2024;7(3):284-289.

Received: 29.03.2024 ◆ **Accepted**: 19.04.2024 ◆ **Published**: 27.05.2024

ABSTRACT

Aims: The aim is to evaluate sonographic parameters in pregnant women diagnosed with carpal tunnel syndrome compared to electrodiagnostic tests, to determine whether these parameters have sufficient accuracy to allow their use in clinical practice.

Methods: This retrospective study examines pregnant women aged 18-40 in the 3rd trimester who received a final diagnosis of carpal tunnel syndrome between 2021-2023 at Prof. Dr. Cemil Taşçıoğlu City Hospital. Pregnant women with symptomatic complaints were divided into two groups: those with positive electrodiagnostic test results indicating carpal tunnel syndrome and those with negative electrodiagnostic test results, forming the control group. All pregnant women participating in the study had their median nerve cross-sectional area, flexor carpi radialis, cross-sectional area, wrist-to-forearm ratio, and MN-CSA/FCR ratio (expressed as a percentage called NTR) values examined.

Results: In pregnant women with carpal tunnel syndrome, the median nerve cross-sectional area values were observed to surpass those in the control cohort (10.06±3.24 vs. 7.84±2.52)($p<0.001$). The wrist-to-forearm ratio in pregnant women with carpal tunnel syndrome (2.1±0.5) was statistically higher compared to the control group (1.0±0.1)($p<0.001$). The NTR values in the pregnant women with carpal tunnel syndrome (CTS) were also higher than those in the control group (0.92±0.36 vs. 0.80±0.23) ($p=0.036$). The best cut-off for median nerve cross-sectional area values was calculated to be >8.6 mm². The best cut-off point for MN-CSA/FCR values was found to be >0.84%. The best cut-off for wrist-to-forearm ratio values was calculated as >1.4 mm². A receiver operating characteristic curve was generated, and the wrist-to-forearm ratio cut-off point of 1.4 showed a sensitivity of 97.1% and a specificity of 69.2%.

Conclusion: Ultrasonography is useful in the diagnosis of pregnancy-related CTS. It has provided comparable results to electrodiagnostic tests and is additionally practical, cost-effective, and swift.

Keywords: Carpal tunnel syndrome, cross-sectional area, ultrasonography

INTRODUCTION

The first records related to carpal tunnel syndrome (CTS) date back to the 1850s; Paget described this syndrome as trap neuropathy in those years, and a century later, in the 1960s, Phalen brought up the much more common form known as idiopathic CTS, increasing recognition of this syndrome.[1] Today, CTS is recognized as the most common peripheral neuropathy, with a reported prevalence ranging from 0.2% to 4% in the general population.[2] While CTS is often idiopathic, various factors have been associated with it, including chronic diseases (such as diabetes mellitus, rheumatoid arthritis, gout, and hypothyroidism) or strenuous repetitive hand movements. Nowadays, vibration occurring in the palm base and chronic mechanical stress, particularly in occupational branches that extensively use the wrist, can lead to CTS.[3]

The exact cause of pregnancy-related carpal tunnel syndrome (PRCTS) is unknown, but it is believed to be related to hormonal changes and local edema in the carpal tunnel.[4] PRCTS symptoms are often bilateral and typically more common in the third trimester.[5] Diagnosis of CTS is made based on history, clinical symptoms, and physical examination. The prevalence of PRCTS based on clinical symptoms ranges from 31% to 62%, while electrodiagnostically confirmed PRCTS ranges from 7% to 43%.[6] Clinical findings may include numbness in the distribution of the median nerve, sometimes accompanied by sensory disturbances, brachialgia paresthetica nocturna, thenar muscle atrophy, and occasionally swelling on the palmar aspect of the wrist. Provocative clinical tests (Phalen/Tinel) can strengthen the diagnosis.[7] Electrodiagnostic (EDx) tests are considered the gold standard, particularly useful when the diagnosis is uncertain, or when there are confusing neurological disorders like radiculopathy or polyneuropathy, or to assess the severity of the disease. However, the invasiveness and false-negative rate of EDx tests have led to the exploration of other, less invasive, and more suitable diagnostic options.[8] Our study aims

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to evaluate practical non-invasive sonographic parameters in pregnant women diagnosed with CTS compared to EDx tests, determining whether these parameters have sufficient accuracy to allow their use in clinical practice.

METHODS

The study was approved by the institutional review board of Prof. Dr. Cemil Taşçıoğlu City Hospital Clinical Researches Ethics Committee (Date:06.02.23 Decision No:87). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study is a retrospective review of pregnant women in their third trimester, aged 18-40, who received a final diagnosis of CTS and presented to the neurophysiology (EMG) laboratory at Prof. Dr. Cemil Taşçıoğlu City Hospital between 2021 and 2023. Our institutional standard for pregnant women with carpal tunnel symptoms relies on a definitive diagnosis based on EDx tests. Patients with clinical symptoms but normal EDx results constituted the control group for our study. Routine wrist ultrasound is performed for patients with a diagnosis. Patients with incomplete clinical examinations or unavailable wrist ultrasound data were excluded from the retrospective data review. Symptomatic evaluations of 76 wrists meeting the study criteria were assessed through the hospital's electronic information system.

Pregnant women presenting with numbness or pain in their wrists undergo routine wrist examinations following regular prenatal check-ups in obstetrics clinics. This examination includes assessment of upper extremity muscle strength, sensation, muscle stretch reflexes, and provocative tests (Phalen and Tinel). A clinical diagnosis of CTS is made based on the presence of symptoms such as wrist pain, tingling in the fingers, numbness, weakness in the abduction or opposition of the thumb, especially in the first three fingers, or positive provocative test results, along with sensory disturbances in the hands. Symptomatic CTS findings referred to the neurophysiology unit undergo routine administration of the Boston Carpal Tunnel Questionnaire (BCTQ). Pregnant women with severe CTS symptoms, including thenar muscle atrophy or a difference of at least 8 mm in two-point discrimination in at least one finger, those who have used a wrist splint in the dominant hand within the past year, received steroid injections for CTS, have inflammatory joint disease, polyneuropathy, experienced trauma to the dominant hand in the past 12 months, undergone CTS surgery, have a bifid median nerve, inability to complete questionnaires due to speech difficulties or cognitive impairment, multiple pregnancies, hypothyroidism, or severe obstetric diseases (uncontrolled gestational diabetes, severe preeclampsia, eclampsia, premature rupture of membranes, or medical conditions requiring urgent delivery), and women with known substance abuse (alcohol or drug) are excluded from the study.

EDx Testing

All nerve conduction studies (NCS) were performed at a skin temperature of 32 °C. For CTS, a minimum of median motor response over the abductor pollicis brevis, median mixed nerve action potential, and ulnar mixed nerve action potential recordings were performed. The median motor nerve conduction study was obtained by placing recording electrodes over the abductor pollicis brevis and stimulating the nerve 6.5 cm proximally at the wrist. Median and ulnar mixed NCS were obtained by stimulating the nerves in the palm and recording 8 cm proximally over the respective nerves. A diagnosis of CTS was defined by a distal motor latency of >4.3 ms, a median mixed nerve latency of >2.2 ms, or a difference between median and ulnar mixed latencies of ≥0.4 ms. Distal median motor latency, median motor compound muscle action potential amplitude, median mixed nerve latency, and median and ulnar mixed inter-latency differences were recorded for all patients.[9]

Ultrasound

Ultrasound examinations were performed within 1 week after electrodiagnostic study. The ultrasound examinations were performed by a neuroradiologist with 25 years of experience in the field of ultrasonography and specialization in musculoskeletal radiology. In the examination, anatomical structures were assessed using a high-resolution US device. These included the median nerve cross-sectional area (MN-CSA), the flexor carpi radialis (FCR) cross-sectional area at the carpal tunnel entrance at the same level, the carpal tunnel inlet (CTI) cross-sectional area, and the cross-sectional areas of the median nerve in the forearm, 12 cm proximal to the wrist. In the measurements, once the location of these specified structures was identified, their circumferences were marked in the axial plane, and the cross-sectional areas were noted in square millimeters (mm^2). US findings were reviewed for median nerve CSA at the distal wrist crease and 12 cm proximal to the distal wrist crease. The wrist to forearm ratio (WFR) of CSA (wrist CSA/forearm CSA) was calculated. This process was performed separately for both wrists (Figure). Patients were assessed with a high-resolution ultrasound device (7-11MHz linear probe, Toshiba Aplio 500, 2017 model, Toshiba Medical System Corporation, Japan).

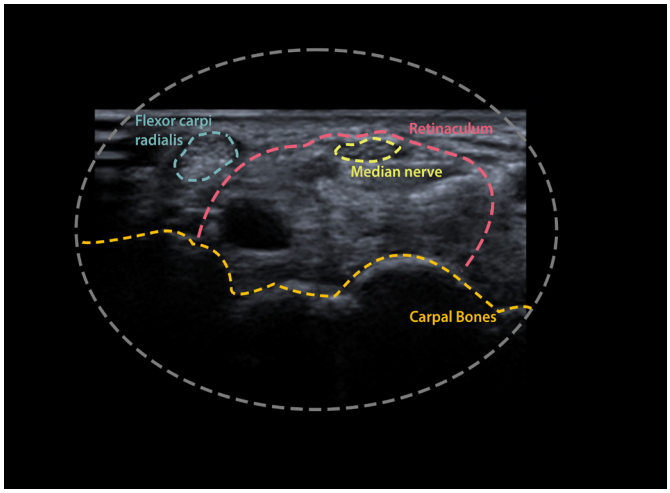

Figure. On the US image obtained at the entrance level of the carpal tunnel in the wrist; flexor carpi radialis and the median nerve were measured. Evaluation was also performed by measuring the wrist circumference at the same wrist.

The patients were seated on a chair opposite the radiologist on the examination table to ensure their comfort. The patient's

arms were positioned on the examination table in a supine position, with their hands placed in a free and neutral position. The radiologist examined while sitting across from the patient on the other side of the examination table. The radiologist was not permitted to ask the volunteers or patients about symptoms to minimize observer bias. Sonographers were blinded to the clinical and NCS outcomes.

Boston Carpal Tunnel Syndrome Questionnaire (BCTQ)

The BCTQ is a questionnaire consisting of a total of 19 questions used to evaluate the severity of symptoms and functional status in patients with CTS. The answers are multiple-choice, and each question is assessed with at least one and up to five points. One point corresponds to the mildest symptom or the best functional capacity, while five points correspond to the most severe symptom or the worst functional status. A high average score for the patient indicates that their complaints are severe or their functional capacity is inadequate. The symptom severity score is the total score obtained from 11 questions. The average symptom severity score is obtained by dividing the total score obtained for all questions by the current number of questions. The functional capacity score is the total score obtained from eight questions. The average functional capacity score is obtained by dividing this total score by eight.[10] The survey has been validated in Turkish.[11]

Statistical Analysis

Descriptive statistics were provided for continuous data, including mean, standard deviation, median, minimum, maximum values, and for discrete data, counts and percentage values were presented. To assess the normal distribution of continuous data, the Shapiro-Wilk test was utilized. For comparing continuous data and ultrasound measurements with the EDx result, the student's T-test was used for normally distributed data, and the Mann-Whitney U test was used for data that did not follow a normal distribution. Group comparisons of nominal variables (in contingency tables) were performed using the Chi-squared test and Fisher's exact test. The diagnostic performance of US measurement values was evaluated using the area under the ROC curve (AUC). The optimal cut-off point was determined using Youden's Index. The diagnostic accuracy criteria for US values (sensitivity, specificity, positive predictive value, negative predictive value) were assessed. For comparing wrist US measurements in patients with pathological results in the EDx, the Kruskal-Wallis variance analysis was used to evaluate differences among those with mild, moderate, and severe conditions. The source of differences was examined through the Kruskal-Wallis multiple comparison test. IBM SPSS for Windows 20.0 (SPSS Inc. Chicago, IL) software was used for the analysis, and a significance level of $p<0.05$ was considered statistically significant.

RESULTS

In our study, the mean ages of the two groups mentioned in the methods section were 32.79±5.38 for the control group with normal EDx results and 33.33±4.41 for pregnant women with CTS. There was no significant difference in age between the groups. There were no differences observed between the groups regarding BMI and parity. Although complaints started earlier in pregnant women with CTS in our study, as only third-trimester pregnant women were included, this difference is not clinically significant from an obstetric standpoint.

In pregnant women with symptoms, the BTCQ scores were found to be 30.59±9.60 in the group with CTS and 14.11±2.49 in the control group. BTCQ scores were significantly higher in the CTS group ($p<0.001$). When evaluated in terms of clinical provocative tests, there was no statistically significant difference observed in Phalen and Tinel signs ($p=0.644$, $p=0.613$, respectively). A family history was more frequently observed in pregnant women with CTS ($p<0.001$). Characteristic features are summarized in Table 1.

Table 1. Demographic data and characteristic features of groups

	EDx normal (n=38) Mean±SD Median; (IQR)	EDx pathologic (n=38) Mean±SD Median; (IQR)	p value
Age (years)	32.79±5.38 (20-43)	33.33±4.41 (20-43)	0.073[a]
BMI (kg/m²)	28.67±4.45 29 (25.21-31.17)	29.23±4.52 28.72 (25.30-31.60)	0.540[c]
Parity median (IQR)	1 (1-2)	1 (1-2)	0.879[c]
Complaint start week	30.99±1.65 31 (30-32)	30.19±1.39 30 (29-31)	0.002[c]
Pregnancy week	31.81±11.89 32 (32-34)	32.86±2.28 33 (32-36)	<0.001[c]
Weight gained during pregnancy	11.86±3.01 13 (11-15)	11.42±3.51 11 (10-13)	0.540[c]
Previous type of birth			
NSD	33 (49.3)	50 (86.2)	<0.001[b]
C/S	34 (50.7)	8 (13.8)	
Family history			
Absent	81 (100)	61 (77.2)	<0.001[b]
Present	0 (0)	18 (22.8)	

EDx: Electrodiagnostic, SD: Standart deviation, BMI: Body mass index, a: Student's T test, b: Chi-square test/Fisher's exact test, c: Mann-Whitney U test

In our study, there was no difference in wrist measurements between the groups. The MN-CSA in the CTS group was found to be 10.06±3.24 mm², which was statistically higher than in the control group ($p<0.001$). The WFR in pregnant women with CTS was 2.1±0.5, statistically higher than in the control group ($p<0.001$). The MN-CSA/FCR (NTR) % values were higher in the CTS group compared to the control group, respectively (0.92±0.36 vs. 0.80±0.23, $p=0.036$). The findings are summarized in Table 2.

Table 2. Comparison of EMG results with wrist ultrasound findings between groups

	EDx normal (n=38) Mean±SD Median (IQR)	EDx pathologic (n=38) Mean±SD Median (IQR)	p value
Wrist circumference	15.43±0.79	15.51±1.03	0.791[c]
Forearm median nerve mm²	4.64±0.75	5.06±1.40	0.100[c]
MN-CSA mm²	7.84±2.52	10.06±3.24	<0.001[c]
FCR mm²	9.66±1.36	11.26±3.28	0.001[c]
WFR	1.0±0.1	2.1±0.5.	0.001[c]
MN-CSA/FCR (NTR) %	0.80±0.23	0.92±0.36	0.036[c]

SD: Standart deviation, c: Mann-Whitney U test, EDx: Electrodiagnostic test, FCR: Flexor carpi radialis, MN-CSA: Median nerve cross-sectional area

The best cut-off for MN-CSA values was calculated as >8.6 mm². A receiver operating characteristic curve was generated, and the MN-CSA cut-off point of 8.6 showed a sensitivity of 58.3% and a specificity of 65.3%. The positive predictive value and the negative predictive value were 71.9% and 72.9%, respectively, with the mentioned point as the diagnostic threshold (area under the curve [AUC), 0.592 (95% confidence interval (CI), 0.637-0.801)]. The best cut-off for WFR values was calculated as >1.4 mm². A receiver operating characteristic curve was generated, and the WFR cut-off point of 1.4 showed a sensitivity of 97.1% and a specificity of 69%. The positive predictive value and the negative predictive value were 56.4% and 78.1%, respectively, with the mentioned point as the diagnostic threshold [area under the curve, 0.582 (95% CI, 0.491-0.673)]. The best cutoff for MN-CSA/FCR values was found to be >0.84%. A receiver operating characteristic curve was generated, and the NTR cut-off point of 0.84% showed a sensitivity of 51.9% and a specificity of 67.9%. The positive predictive value and the negative predictive value were 61.2% and 59.1%, respectively, with the mentioned point as the diagnostic threshold [area under the curve, 0.592 (95% CI, 0.503–0.680)]. The findings are summarized in Table 3.

Table 3. The diagnostic performance of ultrasound findings in predicting carpal tunnel diagnosis (pathological in EDx results)

	AUC (SE) 95% CI	p	Cutoff	Sensitivity 95% CI	Specificity 95% CI	PPV	NPV
MN-CSA mm²	0.719	<0.001	>8.6	0.583	0.653	0.719	0.729
FCR mm²	0.656	0.001	>11.3	0.481	0.901	0.826	0.640
WFR	0.582	<0.001	>1.4	0.971	0.692	0.564	0.781
MN-CSA/FCR (%)	0.592	0.045	>0.84	0.519	0.679	0.612	0.591

FCR: Flexor carpi radialis, WFR: Wrist to forearm ratio MN-CSA: Median nerve cross-sectional area, BCTQ: Boston carpal tunnel questionnaire

DISCUSSION

In our study, we found that WFR, NTR and MN-CSA measurements gave comparable results to electrodiagnostic test results in preganancy CTS.

Our study demonstrated the usefulness of ultrasound measurements in PRCTS due to its non-invasive and practical nature. Pregnancy, with its inherent nature and changing hormonal effects, often leads to CTS. In this context, the impact of pregnancy itself and potential neuropathies on daily life can lead to depressive symptoms in pregnant women.[12] The commonly expressed belief that CTS symptoms will alleviate after childbirth is not always accurate and has been shown in studies. In one study, it was observed that these symptoms could persist for up to 3 years postpartum.[13] This may be attributed to the frequent active use of the wrist during breastfeeding, potentially contributing to edema and inflammation. Another study investigating possible risk factors found that symptoms starting before the third trimester, an increase in the severity of CTS symptoms during pregnancy, and ongoing CTS postpartum were identified as risks.[14]

Although the best diagnostic strategy for CTS remains uncertain, clinical symptoms and physical examination continue to form the basis of diagnosis, but their diagnostic accuracies vary. Our literature review revealed a prevalence of clinically suspected PRCTS ranging from 30% to 60%, while the prevalence of electrodiagnostically confirmed PRCTS varies between 7% and 43%.[15] This variability stems from differences in methodological approaches used across studies, such as the lack of confirmation with EDx testing in PRCTS and widely varying sample sizes (ranging from 15 to 10,000) in systematic analyses.[15] Another crucial point is that clinical parameters and used provocative tests alone may not be sufficient. It has been shown that combining multiple provocative tests enhances the sensitivity and specificity in diagnosing CTS.[16] Although our study did not find a statistical difference between groups in terms of Phalen and Tinel tests, we agree with the literature that these tests strengthen the clinical symptoms for diagnosis.

Especially in cases of PRCTS, alternative ultrasound studies have been of interest for diagnosis or treatment monitoring.[17] Particularly in groups involving pregnant women, familiarity with obstetric ultrasound and the perception of its harmlessness is crucial, especially in populations such as pregnancy that require special attention. In recent years, there has been significant heterogeneity in MN-CSA ranging from 9 to 16.8 mm² in many studies.[18] In a recent study, the diagnostic threshold value was found to be optimal at 11.75 mm².[19] Similarly, in another study, MN-CSA was found to be higher than 9.44±2.68 mm² in the control group, although not confirmed with EDx.[20] In a meta-analysis focusing on this topic, 2292 wrists were examined, with MN-CSA being 11.64 mm² for mild CTS, 13.74 mm² for moderate CTS, and 16.80 mm² for severe CTS (20). In our study, consistent with the literature, MN-CSA >8.6 was found to have a sensitivity of 58% and specificity of 65% for diagnosing CTS in pregnant women. In our literature review, the most commonly studied parameter in CTS is WFR. A WFR of ≥1.4 provided 100% sensitivity for detecting patients with CTS, while using solely the median nerve area at the wrist yielded a sensitivity of 45-93%, contingent on the chosen cut-off value.[21] In another study, a WFR cut-off value of 1.53 mm² resulted in sensitivity and specificity of 60% and 92.5%, respectively, for diagnosing CTS.[22] In our study, consistent with the literature, WFR >1.4 mm² was found to have a sensitivity of 97.1% and specificity of 69% for diagnosing CTS in pregnant women. NTR is a relatively new parameter that has not been extensively studied in pregnant women. In a study conducted in a non-pregnant population, NTR was found to be 0.83%.[23] Especially, the origin of this parameter stems from the search for a new parameter independent of anthropometric measurements, as wrist measurements in CTS are influenced by wrist thickness and a person's height and weight measurements. In this context, it is promising as a new parameter in the face of differences in weight and edema between trimesters in pregnant women. In our study, similar to the relevant study, we found that NTR >84% had a sensitivity and specificity of 52% and 68%, respectively, for diagnosing CTS. Especially in more severe cases requiring postpartum or invasive treatment, examining the performance of NTR will allow us to better test the clinical sensitivity of the relevant parameter in the future. Today, ultrasound has aroused interest as an alternative diagnostic test for CTS.[24] Studies have used EDx or clinical diagnosis as the reference standard while determining the sensitivity and specificity of ultrasound in diagnosing CTS.[25] A meta-analysis revealed that ultrasound exhibited a sensitivity of 77.6% and a specificity of 86.8% in diagnosing

CTS. Notably, these values remained competitive when using EDX as the benchmark (80.2% sensitivity and 78.7% specificity).[26] Technological advancements in ultrasound provide more detailed pathophysiological information about the median nerve and surrounding structures. This information not only enhances diagnostic accuracy but also enriches and complements our understanding of CTS pathology by providing additional insights. However, there are still some challenges in ultrasound assessment. One of these challenges is the need for standardized protocols. Additionally, difficulties arise due to variations in race, gender, and physique, which are important for the diversity of studies, especially when dealing with the median nerve. Investigating the diagnostic significance of ultrasound in patients with diabetes and chronic kidney disease, apart from the pregnant population, will expand our knowledge in this area.[27] Another consideration is the variability in carpal tunnel characteristics, which may necessitate different threshold values for patients with CTS due to these conditions. Furthermore, the relationship between ultrasound findings and the progression of the disease remains unclear. These findings may reflect the pathological anatomy and kinetics associated with CTS. However, it is still unknown whether it is possible to predict outcomes or identify risk factors based on ultrasound findings, and the role of ultrasound examination in decision-making for treatment options remains uncertain. Looking at it from another perspective, when comparing open and endoscopic procedures in compressive carpal tunnel surgery, ultrasound-guided procedures offer advantages in visualizing all important anatomical structures with a small incision and minimal soft tissue damage.[28]

Nerve ultrasound has gained importance in the diagnosis of CTS alongside traditional neurophysiological tests, and emerging imaging techniques such as ultrasound elastography and magnetic resonance tractography further corroborate these findings.[29] We believe that ultrasound radiomics applications, which have recently entered our lives, will continue to be prominent in the future. In a recent meta-analysis, ultrasound radiomics demonstrated superior diagnostic performance in detecting CTS compared to evaluations by radiologists. Additionally, ultrasound radiomics showed minimal variability in diagnostic accuracy even during the training and testing phases, highlighting its potential as a strong diagnostic tool in CTS.[30] While clinical assessment, neurophysiology, and imaging provide supportive evidence, the selection of the most appropriate approach for diagnosis and treatment depends on the clinician's experience. Evaluating the response to treatment based on ultrasound parameters should also be considered in the future.

Among the strengths of our study is the unbiased and comprehensive application of diagnostic tests. Blinding the radiologist and their expertise in the neuromuscular field strengthened our findings.

Despite the introduction of numerous new methods for the diagnosis and treatment of CTS, there is a continued need for well-designed longitudinal studies in the future. These studies are necessary to confirm the effectiveness of these new approaches and evaluate their feasibility in clinical research settings.

Limitations

A limitation of our study arises from the small sample sizes for each group and its retrospective nature. The lack of division into groups based on mild, moderate, and severe CTS is relatively limiting, with the most significant reason being the insufficiently large sample size.

CONCLUSION

Ultrasound applications in PRCTS are non-invasive, practical, cost-effective, and beneficial. MN-CSA, WFR, and NTR have provided comparable results to electrodiagnostic tests.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the institutional review board of Prof. Dr. Cemil Taşçıoğlu City Hospital Clinical Researches Ethics Committee (Date:06.02.23 No:87).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1448006
J Health Sci Med. 2024;7(3):290-295

Distribution and antifungal susceptibility profiles of *Candida* species isolated from dermatomycosis patients

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Cite this article as: Aydın Kurç M, Kaya AD, Erfan G, Albayrak Ş. Distribution and antifungal susceptibility profiles of *Candida* species isolated from dermatomycosis patients. *J Health Sci Med.* 2024;7(3):290-295.

Received: 08.03.2024 ◆ **Accepted**: 21.04.2024 ◆ **Published**: 27.05.2024

ABSTRACT

Aims: Superficial mycoses are the most common dermatological diseases worldwide, and the causes are becoming increasingly resistant to antifungal agents used in treatment. The aim of our study was to identify the yeast species causing superficial mycoses and determine their susceptibilities to some antifungal agents.

Methods: Skin and nail scraping samples obtained from 726 patients with suspected superficial fungal infection were collected and examined by direct microscopy and culture. Isolates were identified by conventional methods and API ID32 C (Biomeriux, France) commercial kits. The minimum inhibitory concentrations (MIC) of isolates against itraconazole, miconazole, nystatin, and terbinafine antifungals were determined by microdilution method.

Results: A total of 59 yeasts were isolated from the samples. The most frequently isolated species were *Candida glabrata* (n=31, 52.54%), *Candida guillermondii* (n=9, 15.25%), and *Candida albicans* (n=7, 11.86%). In terms of infection sites, the most common involvement was observed in the foot (n=39, 66.1%) and nails (n=16, 27.1%). In terms of their antifungal susceptibilities, the highest resistance was detected against terbinafine (35.6%) and itraconazole (33.9%). Multidrug resistance was observed among strains of the *Candida* species (n=17, 28.8%).

Conclusion: The most striking results of this study can be summarized as high rates of *Candida glabrata* isolation, increase in resistance rates, and a prevalence of 28.8% multidrug resistance. This data once again emphasize the importance of isolation, identification, and antifungal susceptibility testing in the diagnosis and effective treatment of superficial mycoses.

Keywords: Superficial mycoses, *Candida* spp., antifungal susceptibility, multidrug resistance

INTRODUCTION

Superficial fungal infections are dermatological diseases effecting hair, nails, and skin and are commonly seen worldwide with a reported prevalence rate of 20-25%.[1] The infectious agents are mostly dermatophytes of the genus *Microsporum*, *Trichophyton* and *Epidermophyton*, yeasts, and rarely non-dermatophytic filamentous fungi.[2]

Dermatophytosis, pityriasis versicolor, and candidiasis are the three most common superficial fungal infections.[3] Dermatophytosis is classified according to the effected body sites as tinea corporis, tinea capitis, tinea pedis, tinea manum, and tinea unguium.

Candidiasis is an infection caused by *Candida* species, members of the human microbiota and can show systemic involvement, as well as involving skin and mucous membranes. Host immune response play a key role in the development of Candidiasis.[3,4] *Candida albicans (C. albicans)* is the most common species responsible from approximately 80-90% of all skin infections caused by *Candida* genus.[5] However, studies suggest more than 50% increase in the frequency of non-albicans *Candida* (NAC) species, including *Candida glabrata (C. glabrata), Candida parapsilosis (C. parapsilosis), Candida tropicalis (C. tropicalis), Candida krusei (C. krusei), Candida lusitaniae (C. lusitaniae), Candida dubliniensis (C. dubliniensis),* and *Candida guilliermondii (C. guilliermondii)*, recently.[6]

The main groups of systemic antifungals commonly used for the treatment of superficial mycoses are imidazoles (ketoconazole), triazoles (fluconazole and itraconazole), and allylamine (terbinafine). Although various antifungals, both topical and systemic, are available today, there is a need for more effective and less toxic new agents.[7] The variations on spectrum of activity of antifungals, drug bioavailability, drug interactions, or resistance can lead treatment failures. The selection of therapeutic agents need to be related with the causative fungal species, the efficacy,

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safety profile, and pharmacokinetics of antifungals.[8,9] Evaluating the susceptibility profile of the antifungal drugs is crucial for treatment.[8]

The most commonly isolated causative agents of superficial mycosis are dermatophytes, followed by yeast species. The identification of these isolates affects the success of treatments due to their different antifungal susceptibility patterns. Therefore, our study aims to identify yeast isolates obtained from skin and nail samples, which are the causative agents of superficial mycoses, and to determine their antifungal susceptibilities.

METHODS

Ethics

Written approval was obtained for this research from the Ethical Evaluation Commission of the Faculty of Medicine in Namık Kemal University (Date: 29.12.2012, Decision No: 2012/05/01/05). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Collection of Samples

In this study, 726 patients who attended to the Dermatological and Venereal Diseases Clinic at Namık Kemal University Hospital, over a period of 18 months (between 11.10.2011 and 08.04.2013) and suspected of superficial fungal infections were included. Skin and nail scraping samples of these patients were collected, and sent to the Microbiology Laboratory. Infected areas were cleaned prior to sampling; a sterile scalpel was used to collect from the corners of skin lesions, while for nail lesions scraping samples were collected until healthy tissues were reached and the samples were transferred into sterile petri dishes. The samples were used for direct microscopic examination and culture inoculations.

Direct Microscopic Examination

Samples were placed on a clean slide, 10-20% KOH (Potassium hydroxide) solution was added, the slide was covered and pressed slightly, and was finally incubated at room temperature for 15-30 minutes for examination. The examination was conducted under the microscope sequentially at a magnification of x10 and x40, and the presence of spores (arthrospores, blastospores, etc.) and hyphae was investigated in all microscopic fields.[10] The microscopic examination was regarded as positive in the presence of any of these structures.

Culturing and Identification of Samples

Multiple inoculations were carried out from the collected samples on Sabouraud Dextrose Agar (SDA) (Merck, Germany) in addition to SDA containing chloramphenicol, cycloheximide, and gentamicin and Potato Dextrose Agar (PDA) (Oxoid, England). All media were incubated for four weeks in an incubator, at 26°C and 37°C. The cultures were checked twice a week and evaluated for fungal growth. Germ tube test was conducted for yeast isolates and their microscopic appearances in Corn Meal-Tween 80 agar (Corn Meal Agar, Beckton Dickinson, USA) were evaluated,[11] followed by identification using API ID32 C (Biomeriux, France) commercial kits.

Antifungal Susceptibility Test

Isolated yeasts were tested for their susceptibilities to the antifungals itraconazole, miconazole, nystatin, and terbinafine. MIC ranges of the antifungal drugs were set between 0.0313-16 µg/mL. Reference microdilution method was applied using RPMI 1640 (Sigma Chemical Co., St. Louis, Mo, USA) containing L-glutamine and without bicarbonate, in order to evaluate susceptibility. After adding 2% dextrose and adjusting the pH to 7.0 using 0.165 M morpholine-propane-sulphonic acid (MOPS, Sigma), this medium was used in Broth Microdilution (BMD) test. *C. albicans* (ATCC 90028), *C. glabrata* (ATCC 90030), *C. parapsilosis* (ATCC 22019), *C. krusei* (ATCC 6258), and *C. tropicalis* (NRRL Y-12968) were used as quality control strains. For the preparation of yeast suspensions, colonies from 24-hour SDA were collected and prepared as homogeneous suspensions in sterile physiological saline and turbidity was adjusted to 0.5 McFarland. After the addition of certain antifungals, media, and yeast suspensions, the micro-plates were incubated at 35°C for 48 hours, and MIC values were evaluated according to the MIC values specified in the M27-S3 and M27-S4 guidelines prepared by "Clinical Laboratory Standards Institute (CLSI)".[12,13] Breakpoints were set by CLSI for azoles as follow; itraconazole (susceptible, MIC≤0.125 µg/ ml; dose dependent, 0.25-0.5 µg/ml; resistant, MIC≥1 µg/mL). Miconazole does not have a specified breakpoint; nonetheless, literature indicates that *Candida* species is susceptible at MIC≤5 µg/mL and resistant at MIC≥5 µg/mL, respectively. According to the literature, terbinafine susceptibility limit values are evaluated as ≤8 µg/mL sensitive and >8 µg/mL resistant.[14-17]

RESULTS

In our study, yeasts were detected in 59 (8.1%) of the skin and nail scraping samples of 726 patients. The average age of patients considered for evaluation was determined as 51.72±14.85 (19-80 years). 39 (66.1%) of the cases were male patients, while 20 (33.9%) were female patients.

When the samples obtained from patients having yeast growth were examined according to the distribution of infected sites, the most common involvement was observed in the foot (n=39, 66.1%) and nails (n=16, 27.1%), followed by the trunk (n=2, 3.4%) and hands (n=2, 3.4%).

In direct microscopic examination using KOH of a total of 59 samples having yeast growth, direct microscopic positivity were detected in 37 (62.7%) of the cases, while 22 cases resulted with direct microscopic negativity (37.3%).

When examining the samples with positive germ tube test and Cornmeal-Tween 80 agar morphology, 31 samples were identified as *C. glabrata* (52.54%), 9 as *C. guillermondii* (15.25%), and 7 as *C. albicans* (11.86%). The distribution of yeasts is given in Table 1.

The results of in vitro antifungal susceptibility tests (MIC range, MIC50 and MIC90) of four antifungals against all yeast isolates are shown in Table 2. According to the antifungal susceptibility test, 11 (18.6%) isolates were found to be dose-dependently susceptible and 20 (33.9%) isolates were found to be susceptible (8 *C. glabrata*, 4 *C. albicans*, and

2 *C. guillermondii*) to itraconazole. Our results indicate that a total of 10 (16.9%) isolates, four of which are *C. glabrata*, two are *C. albicans*, *C. guillermondi, C. krusei, C. lusianiae*, and one *C. tropicalis* isolate were resistant to miconazole. Terbinafine MIC values indicate that 21 (35.6%) strains were resistant (12 *C. glabrata* and 4 *C. albicans*). Moreover, according to our results, multidrug resistance was observed among strains of the *Candida* species (n=17, 28.8%). Multidrug resistance was observed in 8 *C. glabrata*, 3 *C. albicans*, 1 *C. guillermondii*, and 1 *C. krusei* isolates.

Table 1. The distribution of isolated yeasts

Yeast	n	%
Candida glabrata	31	52.54
Candida guillermondii	9	15.25
Candida albicans	7	11.86
Candida tropicalis	4	6.77
Candida dubliniensis	2	3.38
Candida keyfr	1	1.69
Candida krusei	1	1.69
Candida lusitaniae	1	1.69
Candida parapsilosis	1	1.69
Candida zeylanoides	1	1.69
Rhodotorula spp.	1	1.69

DISCUSSION

Superficial mycoses are infections of the keratinized tissues of humans and animals, including the skin, nails, and hair.[18] Epidemiological studies indicate that they are the most common infections worldwide, affecting all age groups and leading to high expenditures for treatment every year.[7] Although dermatophytoses are the most common fungal infection in humans among superficial mycoses, candidiasis and pityriasis versicolor are also quite prevalent.[19]

Superficial mycoses epidemiology can be influenced by many factors such as geography, climate, historical factors, migration, wars, quality of health services, society's educational level in the region, and social factors.[20] When the distribution according to patient age groups was examined in previously conducted studies, it was stated that infection varied between the ages of 2 months and 81 years,[21,22] while the average age was between 38 and 40.[23,24] The average age of patients included for evaluation in our study was determined as 51.72±14.85 (19-80).

Many studies conducted in our country show that the majority of the patients with a preliminary diagnosis of superficial mycosis are male.[25-29] These data are consistent with our study as well.

Traditional and phenotypic methods are widely used for diagnosing pathogenic yeasts in clinical laboratories. However, these methods are limited in terms of identifying the isolates at the species level.[30,31] Microscopic examinations using KOH in our study led to direct microscopic positivity in 37 (62.7%) cases out of a total of 59 samples with yeast fungal growth, while direct microscopic negativity was detected in 22 (37.3%) of the cases.

Table 2. Antifungal susceptibility results of yeasts (MIC)

Antifungals	MIC µg/ml		
	MIC range	MIC_{50}	MIC_{90}
C. glabrata (n=31)			
Itraconazole	0.0313-≥16	0.0313	8
Miconazole	0.0313-≥16	0.0625	16
Terbinafine	0.0313-≥16	0.125	16
Nystatin	0.0313-≥16	0.125	8
C. guillermondii (n=9)			
Itraconazole	0.0313-≥16	0.0313	16
Miconazole	0.0313-4	0.5	4
Terbinafine	0.0313-2	0.125	2
Nystatin	0.0313-8	0.5	4
C. albicans (n=7)			
Itraconazole	1-≥16	0.5	16
Miconazole	2-≥16	0.25	8
Terbinafine	0.0313-≥16	4	16
Nystatin	0.0313-8	2	8
C. tropicalis (n=4)			
Itraconazole	0.0625-≥16	0.0625	0.25
Miconazole	0.0313-8	0.0131	4
Terbinafine	0.0313-4	0.0313	0.125
Nystatin	0.0313-8	0.125	4
C. dubliniensis (n=2)			
Itraconazole	0.0313-0.25	-	-
Miconazole	0.0313-0.5	-	-
Terbinafine	0.0313-2	-	-
Nystatin	0.0313-8	-	-
C. kefyr (n=1)			
Itraconazole	1	-	-
Miconazole	0.0313	-	-
Terbinafine	0.0313	-	-
Nystatin	0.0313	-	-
C. krusei (n=1)			
Itraconazole	≥16	-	-
Miconazole	8	-	-
Terbinafine	≥16	-	-
Nystatin	4	-	-
C. lusitaniae (n=1)			
Itraconazole	≥16	-	-
Miconazole	≥16	-	-
Terbinafine	≥16	-	-
Nystatin	4	-	-
C. parapsilosis (n=1)			
Itraconazole	1	-	-
Miconazole	2	-	-
Terbinafine	≥16	-	-
Nystatin	4	-	-
C. zeylanoides (n=1)			
Itraconazole	4	-	-
Miconazole	2	-	-
Terbinafine	8	-	-
Nystatin	0.0313	-	-
Rhodotorula spp. (n=1)			
Itraconazole	0.125	-	-
Miconazole	0.25	-	-
Terbinafine	0.0625	-	-
Nystatin	0.25	-	-

MIC: Minimum inhibitor concentration

While differences in the localization of the lesions have been observed in previous studies, the foot region followed by nails is the most commonly affected localization in many studies. Out of studies conducted in our country, Bilgili and colleagues[26] found that lesions were most commonly in the foot's sites (45%) followed by nails (41.3%) and groin (6.8%); while Ergin and colleagues[25] determined it to be foot (49.8%) followed by nails (25.3%) and trunk (11.9%), and finally Köktürk and colleagues[32] determined it to be foot (54.1%), nails (21.6%), and groin (14.3%). In line with these results, in our study, body sites attacked by yeasts were most commonly the foot (66.1%) and nails (27.1%).

Khodadadi and colleagues[33] mentioned that candidiasis as the most common superficial fungal infection, with a prevalence of 40.5%. Other studies similarly suggested candidiasis prevalence higher in Brazil (82.9%)[30] and Southeast Serbia (57%).[34] This prevalence was determined as 8.1% in our study.

C. albicans is the most commonly identified species as a causative agent among all *Candida* species. However recent studies show that there is an increase in the frequency of *Candida* non-albicans species, particularly *C. glabrata* and *C. parapsilosis*, in superficial fungal infections.[35] The prevalence of *C. glabrata* has increased significantly in the United States over the past decade, being isolated as the causative agent of candidemia in 20-24% of cases.[36] Previous studies have reported *C. albicans* as the most common cause of candidiasis, while *C. glabrata* and other species such as C. *tropicalis* and *C. krusei* as important pathogens.[37,38] The most commonly isolated species in our study are *C. glabrata, C. guillermondii*, and *C. albicans*.

Resistance to commonly used antifungal agents in the treatment of *Candida* infections limits treatment options recently. The most effective approach in the treatment of *Candida* infections is the identification of the isolated yeasts to the species level, followed by susceptibility testing to contribute to the selection of appropriate treatment methods. This, helps prevent the spread of resistant strains and reduces unnecessary drug use.[39] Our results indicate that 35.6% of the isolates were resistant to terbinafine. It was determined that 38.7% of *C. glabrata* strains were resistant to terbinafine, and their MIC values were also found to be quite high. Another study reports that 80% of *C. glabrata* strains were resistant to terbinafine.[38] Although terbinafine exhibits good activity against dermatophytes, it has lower activity against *Candida* species compared to azoles.[40,41] Additionally, these high resistance rates are thought to be caused by the weak inhibitory activity of terbinafine against all *Candida* species except for *C. parapsilosis*.[42,43]

Itraconazole, a member of the azole group, is effective against most *Candida* species, but shows higher MIC values for *C. glabrata* and *C. krusei*.[44] Our study results show that the resistance rates for miconazole and itraconazole of the azole group were 16.9% and 33.9%, respectively. Additionally, 18.6% of the isolates were determined to be dose-dependently susceptible to itraconazole. In a study conducted by Bilal and colleagues,[38] miconazole resistance was found to be 30.4% and itraconazole resistance was 16.1% for *C. albicans*, while miconazole resistance was detected as 8.33% for *C. glabrata* strains (41.67% of which were dose-dependent susceptibility), with no observed resistance against itraconazole. The occurrence of resistance to miconazole is attributed to inappropriate use as a topical therapeutic agent in the treatment of candidiasis.[45] Furthermore, the high resistance to azoles is attributed to their inappropriate use in both agricultural and clinical settings. Additionally, mutations in genes encoding the drug target are common in *Candida* and non-dermatophyte molds, including *Aspergillus* species.[46]

As s polyene derivative, nystatin has become a topical medication that can be used without causing toxic side effects when applied orally, as it is not absorbed from the gastrointestinal tract.[39] When examining studies conducted on nystatin; Agbulu and colleagues[47] claimed to have found the MIC level for *C. albicans* to be 3.13 µg/mL in their research. In another study, the MIC ranges for nystatin were determined as follows: 0.078-10 µg/mL for *C. albicans*, 0.156-1.25 µg/mL for *C. parapsilosis*, 0.156-2.5 µg/mL for *C. tropicalis* and *C. glabrata,* and 0.156-0.625 µg/mL for *C. krusei*.[48] In our study, the MIC ranges were determined to be 0.0313≥16 µg/mL for *C. glabrata*, 0.0313-8 µg/mL for *C. guillermondii*, and 0.0313-8 µg/mL for *C. albicans*.

The Centers for Disease Control and Prevention (CDC) highlights the rise of multidrug-resistant *Candida* and *Aspergillus* species in their latest updates.[49] Acquired resistance to both azoles and echinocandins, either alone or in combination, has been observed, similar to that in *C. glabrata*.[50] A 28.8% prevalence of multidrug resistance was detected in our study. This may be related with the presence of high numbers of *C. glabrata* isolates in our study.

CONCLUSION

Our study aimed to determine the species-level distribution of yeasts and their susceptibility to various antifungal agents in superficial mycoses, which are the important causes of dermatological diseases that are widely prevalent worldwide and pose challenges in treatment. As the distribution of causative agents and their susceptibilities to antifungal agents and the prevalence of superficial fungal infections varies, our study results with limited number of isolates reflects only the data of a medical center in the Thrace region and can not be generalized, which may be accepted as the limitation of the current study. The most striking findings can be summarized as high rates of *C. glabrata* isolation, and increase in resistance rates, and a prevalence of 28.8% multidrug resistance. In this study results once again emphasize the importance of isolation, identification, and antifungal susceptibility testing in the diagnosis of superficial mycoses, which will lead success in treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Namık Kemal University Faculty of Medicine Ethical Evaluation Commission (Date: 29.12.2012, Decision No: 2012/05/01/05).

Informed Consent

Due to the nature of the study, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
This research was funded by Namık Kemal University Scientific Research Projects Coordination Unit, Grant Number NKUBAP.00.20.AR.12.05.

Author Contributions
All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1457042
J Health Sci Med. 2024;7(3):296-300

Investigation of the relationship between fatigue with vitamin D, disease stage, anxiety and physical activity level in patients with Parkinson's disease

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Cite this article as: Yetiş A, Canlı M, Kuzu Ş, et al. Investigation of the relationship between fatigue with vitamin D, disease stage, anxiety and physical activity level in patients with Parkinson's disease. *J Health Sci Med.* 2024;7(3):296-300.

Received: 22.03.2024 ◆ **Accepted**: 01.05.2024 ◆ **Published**: 27.05.2024

ABSTRACT

Aims: The aim of this study was to investigate the relationship between fatigue severity with vitamin D level, disease stage, anxiety and, physical activity level in patients with Parkinson's disease (PD).

Methods: This study included 66 (male=38, female=28) individuals diagnosed with PD. Fatigue severity was evaluated by the fatique severity scale, vitamin D level by blood test results, anxiety by the Beck Anxiety Inventory (BAI), disease stage by Hoehn-Yahr (HY) staging, and physical activity level by the International Physical Activity Questionnaire (IPAQ-short form).

Results: The study included 66 (male=38, female=28) individuals diagnosed with PD. Fatigue severity was assessed by the fatique severity scale, vitamin D level by blood test results, anxiety by the BAI, disease stage by HY staging, and physical activity level by the IPAQ-short form. In addition, a significant correlation was found between fatigue severity with vitamin D level, anxiety, disease stage, and physical activity level in men, women, and all patients ($p<0.05$).

Conclusion: In Parkinson's patients, fatigue may be related to disease stage, anxiety, physical activity level, and vitamin D level. We suggest that these results should be taken into consideration in fatigue coping strategies for patients with PD.

Keywords: Fatigue, vitamin D, anxiety, physical activity, Parkinson's

INTRODUCTION

Parkinson's disease (PD) is among the most prevalent neurodegenerative conditions, stemming from a combination of environmental and genetic factors, and characterized by gradual progression over time. It comprises motor and sensory symptoms attributed to the degeneration of dopaminergic neurons in the substantia nigra.[1] Its global prevalence stands at approximately 3.28 percent,[2] while in Turkiye, it is around 1.1 percent.[3]

In PD, primary motor symptoms include tremor, rigidity, postural instability, akinesia, and bradykinesia. Secondary symptoms include slowing of activities of daily living, spasticity, mask face, gait disturbances, and kinesiophobia.[4]

Current studies emphasize that sensory symptoms such as depression, cognitive disorders, and fatigue are common in PD in addition to motor symptoms.[5] Since the concept of fatigue in PD was first emphasized by James Parkinson, studies explaining the prevalence, pathophysiology, and impact of fatigue have been carried out in the following periods.[6] The incidence of fatigue was reported to be 33-58% higher in PD patients compared to their healthy counterparts in the study conducted by Freidman et al.[6] Other studies have shown that fatigue is one of the most important barriers to participation in activities of daily living for patients with PD.[7] It has been reported that physical exertion, sleep disorders, inadequate rest, vitamin D levels, and depression levels are associated with physical fatigue in patients with PD.[8,9]

Nowadays, fatigue in patients with PD is an important parameter for research and clinically relevant.[10] The impact of fatigue on the quality of life of people with PD is well known. However, the etiology and pathogenesis of the disease need to be better understood. Many factors (biological, psychosocial, clinical, etc.) may play a role in the development of fatigue in PD.[9,11,12] It is important to elucidate these factors to prevent fatigue. To date, studies have not sufficiently examined the factors associated with fatigue in PD.

This study aimed to investigate the relationships between fatigue severity with vitamin D level, disease stage, anxiety, and physical activity level in patients with PD.

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METHODS

This study involved individuals diagnosed with PD and was approved by the Muş Alparslan University Scientific Researches and Publication Ethics Committee (Date: 07.03.2024, Decision No: 53), conducted in adherence to the Declaration of Helsinki. Prior to the commencement of the study, informed consent, both verbal and written, was obtained from all participants. The study included 66 individuals diagnosed with PD who applied to Kırşehir Ahi Evran University Neurology Outpatient Clinic. Inclusion criteria were as follows: (1) being diagnosed with PD by a specialist neurologist; (2) not having any additional neurologic or orthopedic disorders; (3) having a mini-mental status test score of 24 or above; and (4) voluntarily agreeing to participate in the study. Individuals who were taking medication for depressive symptoms, scored 5 points according to Hoehn-Yahr (HY) staging, could not be contacted, and had conditions that may affect fatigue (such as thyroid dysfunction, anemia, and cardiac problems that may cause physical exertional impairment) were not included in the study.

Evaluation Tools

Demographic information such as age, gender, body mass index, and disease duration was recorded before clinical evaluations. Fatigue level was assessed by the Fatique Severity Scale (FSS), vitamin D level by a blood test, disease stage by HY staging, anxiety level by the Beck Anxiety Inventory (BAI), and physical activity level by the International Physical Activity Questionnaire (IPAQ-short form).

Fatigue severity: In patients with PD, fatigue is a factor that negatively affects the functional status and quality of life of patients. The FSS is a valid and reliable scale for assessing the severity of fatigue in patients with PD, and its use is recommended in the literature.[13,14] In this study, the FSS was used to evaluate severity of fatigue in patients with PD. The FSS assesses fatigue with nine questions. Each question is scored from 0 (strongly disagree) to 7 (agree). The total number of points is obtained by dividing the sum of the points obtained from each of the questions by 9. A high score on the scale indicates an increased severity of fatigue.[13,14]

Vitamin D level: Vitamin D levels of patients with PD were evaluated by HPLC method using Chroms Systems Kit on an Agilent 1200 device. The score obtained from the device was recorded in ng/ml.[15]

Disease stage: HY staging was used to evaluate the stage of PD. According to HY staging, PD are divided into five stages.[16]

Anxiety level: Patients' anxiety levels were assessed using the Turkish version of the BAI.[17] The BAI assesses patients' anxiety levels and consists of 21 questions. Each question is rated from 0 (none) to 3 (severe). The maximum number of points that can be obtained from the scale is 63, and a high number of points indicates the presence of severe anxiety.[18]

Physical activity level: The physical activity level of patients with PD was assessed using the IPAQ-short form. The questionnaire consists of 7 questions assessing the time patients spent physically in the last 1 week. The criterion for physical activity was at least 10 minutes at a time. The duration of vigorous and moderate physical activity, walking, and sitting time were recorded. Sitting time was calculated separately as sedentary behavior. The "MET-minutes/day" score was obtained by multiplying minutes, days, and metabolic equivalent task (MET) values. A total physical activity score was obtained by multiplying 3.3 METs by walking time, 4 METs by moderate physical activity, and 8 METs by vigorous physical activity. A total score below 600 MET-min/week was defined as low level physical activity, 600-3000 MET-min/week as moderate level, and above 3000 MET-min/week as high level physical activity.[19]

Statistical Analysis

SPSS (Version 25.0. Armonk, NY, IBM Corp.) software was used to perform statistical analyses. In statistical analysis process, the results are represented as mean±standard deviation for continuous variables. For nominal variables, numbers and % were used. In order to carry out the signifance tests between genders, the independent samples t-test is applied with α=0.05 level. Factors associated with fatigue severity were evaluated by Pearson correlation analysis in parametric conditions. The correlation degree was interpreted as follows: low correlation from 0.05 to 0.4, moderate correlation from 0.4 to 0.7, and high correlation from 0.7 to 1.0, based on the correlation coefficients.[20]

RESULTS

The demographic data and the clinical evaluation of the patients with PD are shown in Table 1. Mean age of patients enrolled in this study was 69.48±9.74 years.

Table 1. Demographic characteristics of the participants

Variables	Mean±SD	Minimum	Maximum
Age (years)	69.48±6.74	41.00	87.00
BMI (kg/m^2)	25.57±1.70	21.56	30.03
Duration of disease (years)	4.61±2.73	1.00	10.00
Vitamin D level (ng/ml)	21.65±4.20	4.00	56.00
FSS	4.23±1.43	1.80	7.00
HY staging	2.58±0.84	1.00	4.00
BAI	29.39±6.41	10.00	52.00
IPAQ-short form (metabolic equivalent task)	624.06±76.66	400.00	850.00

SD: Standart deviation, BMI: Body mass index, HY: Hoehn-Yahr, IPAQ: International physical activity questionnaire, FSS: Fatique severity scale, BAI: Beck anxiety inventory

The comparison of the variables of Parkinson's patients included in the study according to gender is given in Table 2. According to this table, no statistically significant difference was found for any variable when comparing all variables of patients by gender (p>0.05).

The relationship between fatigue severity and other variables in females, males, and all patients included in the study is given in Table 3. When the relationship between the severity of fatigue in male Parkinson's patients and other variables

was examined, it was found that there was a negative, high-level statistical relationship between the severity of fatigue and vitamin D and physical activity levels of male patients, while there was a positive, high-level statistical relationship between disease stage and anxiety severity ($p<0.05$) (Table 3).

Table 2. Comparison of variables of patients with PD according to gender

Variables	Male (n=38) Mean±SD	Female (n=28) Mean±SD	t	p
Age (years)	71.42±8.62	68.86±7.68	1.921	0.059
BMI (kg/m²)	25.64±1.90	25.47±1.43	0.384	0.703
Duration of disease (years)	4.32±3.24	5.00±4.35	-0.733	0.466
Vitamin D level (ng/ml)	19.66±3.06	24.36±5.25	-1.710	0.092
FSS	4.44±1.39	3.95±1.48	1.369	0.176

PD: Parkinson's disease, SD: Standard deviation, BMI: Body mass index, FSS: Fatique severity scale, t: Independent samples t-test

Table 3. Examination of the relationship between fatigue severity and other variables in female, male and all patients included in the study

Variables		Male (n=38) FSS	Female (n=28) FSS	All patients (n=66) FSS
Age (years)	r	-0.014	-0.021	0.023
	p	0.934	0.916	0.856
BMI (kg/m²)	r	-0.153	0.118	-0.043
	p	0.360	0.551	0.730
Duration of disease (years)	r	0.134	-0.075	0.011
	p	0.424	0.705	0.929
Vitamin D level (ng/ml)	r	-0.791	-0.908	-0.851
	p	<0.001*	<0.001*	<0.001*
HY staging	r	0.897	0.854	0.879
	p	<0.001*	<0.001*	<0.001*
BAI	r	0.845	0.723	0.797
	p	<0.001*	<0.001*	<0.001*
IPAQ-short form (metabolic equivalent task)	r	-0.808	-0.695	-0.757
	p	<0.001*	<0.001*	<0.001*

FSS: Fatique severity scale, BMI: Body mass index, HY: Hoehn-Yahr, BAI: Beck anxiety inventory, IPAQ: International physical activity questionnaire, r: Pearson correlation coefficient, *p<0.001

Similarly, when the relationships between the severity of fatigue and other variables in female Parkinson's patients included in the study were examined, it was found that there was a negative, high-level statistical correlation between the severity of fatigue and vitamin D and physical activity levels of female patients, while there was a positive, high-level statistical relationship between disease stage and anxiety severity ($p<0.05$).

When the relationships between fatigue severity and other variables in all PD patients were examined, it was found that there was a negative, high-level statistical relationship between fatigue severity and vitamin D and physical activity levels, while there was a positive, high-level statistical relationship between disease stage and anxiety severity ($p<0.05$)(Table 3).

DISCUSSION

This study investigated relationships between the severity of fatigue with age, BMI, disease duration, vitamin D level, disease stage, anxiety level, and physical activity level in patients with PD. Significant relationships were found between fatigue severity and vitamin D level, disease stage, anxiety level, and physical activity level in patients with PD. Additionally, when compared in terms of gender in Parkinson's patients, there was no difference in these parameters between male and female participants.

In a review of the literature, Koçer et al.[21] examined the motor and non-motor symptoms related to fatigue in patients with PD and divided Parkinson's patients into three groups: fatigued, non-fatigued, and all Parkinson's patients. They found that there were no significant differences between the groups regarding gender, disease duration, or age also concluded that male Parkinson's patients had less fatigue compared to female Parkinson's patients, but this trend was not significant.[21] In another study, Herlofson and Larsen[22] and Martinez Martin et al.[23] reported that age and disease duration were not significantly related to fatigue severity. In this study, we concluded that there was no significant relationship between severity of fatigue with duration of disease, age and that there was no significant difference in the severity of fatigue between male and female PD patients.

Decreased vitamin D levels are frequently observed in patients with PD. It has been observed that the vitamin D levels of Parkinson's patients are considerably reduced compared to healthy individuals.[24] Zhang et al.,[8] when they compared Parkinson's patients and healthy individuals, stated that vitamin D levels were lower in Parkinson's patients, but they said that vitamin D levels were not related to fatigue severity in Parkinson's patients. Sleeman et al.[25] found that low vitamin D levels were associated with disease severity in Parkinson's patients. Moghaddasi et al.[26] concluded that low vitamin D levels in Parkinson's patients were associated with the severity of motor effects such as postural instability, postural anomalies, and freezing gait. In this study, a negative relation was found between severity of fatigue and vitamin D level which may be attributed to the fact that a low vitamin D level in Parkinson's patients causes abnormal motor movements and consequently more energy consumption in participation in activities of daily living.

In PD, fatigue is one of the most prevalent non-motor symptoms that can be present in the early stages of the disease, often persisting after initial onset, and gradually worsening over time.[27] As a consequence, fatigue can limit Parkinson's patients' participation in activities of daily living as well as negatively affect their quality of life.[27] There is no clear understanding of the pathological conditions that cause PD or the mechanisms by which they cause fatigue. Herlofson and Larsen[22] reported that fatigue in PD is associated with disease stage. Elbers et al.[28] evaluated the disease stage using HY staging in a study conducted in idiopathic Parkinson's patients. They found a significant relationship between disease stage and fatigue severity in idiopathic Parkinson's patients.[28] Other studies have also shown a relationship between disease stage and fatigue severity.[10,29] This study results are consistent with the literature. In this study, a significant relation was observed between fatigue severity and disease stage in men, women, and all Parkinson's patients. We may attribute this result to the worsening of motor symptoms in parallel with the increase in disease stage, which increases the severity of fatigue.

Studies have shown that psychological treatment of both motor and non-motor symptoms in people with

PD is effective in improving both cognitive and physical symptoms.[30] There are studies showing that fatigue in PD is associated with psychological factors such as anxiety, sleep disorders, depression, and apathy.[31] Siciliano et al.[32] stated that psychological factors may be related to fatigue in patients with PD. Gołąb-Janowska et al.[33] reported that depression was associated with fatigue severity in idiopathic Parkinson's patients. In another study, Havlikova et al.[10] evaluated the severity of fatigue in Parkinson's patients with a multidimensional fatigue inventory. When the study findings were analyzed, it was concluded that fatigue severity was related to anxiety and depression levels.[10] In the present study, a significant relationship was found between fatigue and anxiety severity in Parkinson's patients. This result may have occurred due to the abnormal activity and connections of limbic-cortical circuits and the degeneration of serotoninergic pathways.[34,35]

In the literature, studies examining fatigue severity and physical activity levels in patients with PD have shown different results. Increased physical activity in patients with PD has been shown to increase physiological stress. This has been related to increased fatigue severity.[36] Gaerber and Friedman[37] concluded that the increase in the severity of fatigue in patients with PD was related to a low level of physical activity. Increased fatigue severity in idiopathic PD patients was reported to be associated with lower physical activity levels.[28] Lana et al.[38] stated that fatigue severity was not a predictive factor of physical activity level. In the current study, a significant negative relationship was found between fatigue severity and physical activity level in Parkinson's patients. Despite these results, it is still controversial whether fatigue is the cause or consequence of decreased physical activity levels.

Limitations

This study has several limitations. The first is that there was no control group in our study to compare the clinical, biological, and psychological evaluations of Parkinson's patients with their healthy peers. Another limitation is that we did not question the type of PD in patients. In future studies, it may be useful to examine the factors associated with fatigue in PD according to different PD types.

CONCLUSION

In the present study, which investigated the factors associated with fatigue in patients with PD, vitamin D level, disease stage, anxiety, and physical activity level were found to be associated with fatigue severity. We suggest that factors associated with fatigue severity should be taken into consideration when designing treatment programs and evaluating the effectiveness of interventions in patients with PD.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Muş Alparslan University Scientific Researches and Publication Ethics Committee (Date: 07.03.2024, Decision No: 53).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1450444
J Health Sci Med. 2024;7(3):301-307

Comparison of obesity and physical activity levels of adult individuals by examining dietary habits with different parameters

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Cite this article as: Uğurlu D, Yapıcı H, Ünver R, Gülü M. Comparison of obesity and physical activity levels of adult ınıdividuals by examining dietary habits with different parameters. *J Health Sci Med.* 2024;7(3):301-307.

Received: 10.03.2024 ◆ **Accepted**: 03.05.2024 ◆ **Published**: 27.05.2024

ABSTRACT

Aims: The aim of this study was to examine the dietary habits of adult individuals in detail at the level of different variables and to analyze these habits in depth in terms of obesity and physical activity levels.

Methods: In the study, quantitative research methods and a descriptive survey model from general survey designs were used. The research group consisted of 704 adult individuals in Kırıkkale province. The Three-Factor Eating Questionnaire (TFEQ) was used in the study. This is a questionnaire that measures the eating habits of individuals. It was translated into Turkish by Kıraç et al. in 2015 under the name of "TFEQ" and its validity and reliability were proven, and its use in our country was ensured. The questionnaire consists of 18 items. The questionnaire measures the degree of consciously restricting their eating, the level of uncontrolled eating, and the degree of eating when they are emotional. The questionnaire also measures the level of sensitivity to hunger. In this respect, the questionnaire is related to obesity. Since the data were distributed as normal binary, they met the prerequisites for parametric tests. For this reason, an independent sample t test was used for pairwise group comparisons, and an ANOVA test was used for comparisons of three or more groups. In addition, if there was a significant difference in the ANOVA results, the Tukey post hoc test, one of the multiple comparison tests, was applied to determine which groups the difference was between.

Results: It was found that men tended to eat when they were more emotional than women, and those who lived in urban areas, did not smoke or drink alcohol, did not have chronic diseases, had a good economic status, and did more physical activity per week had favorable three-factor nutrition levels.

Conclusion: The findings of the study reveal that variables such as gender, place of residence, smoking and alcohol use, chronic disease, and economic status have significant effects on nutritional behaviors.

Keywords: Three factor nutrition, physical activity, obesity

INTRODUCTION

Obesity, which has caused serious health problems from the past to the present, is defined as the excess of calories obtained through food compared to the calories that the body spends at a normal level, and this excess is stored as fat.[1] Physically sedentary lifestyles, fast-paced work lives, and changes in eating habits cause many adults to experience difficulties in weight control.[2,3] In recent years, obesity has emerged as a serious health problem worldwide.[4,5] For this reason, it has become a serious factor that can negatively affect not only the physical health of the individual but also the quality of life and overall life expectancy.[6]

Obesity has negative effects on the endocrine system, cardiovascular system, respiratory system, gastrointestinal system, skin, genitourinary system, and musculoskeletal system.[7] According to the World Health Organization, obesity causes cardiovascular diseases, diabetes, cancer, and many musculoskeletal disorders.[8] Each year, the World Health Organization (WHO) reports that more than 2.8 million adults die due to overweight or obesity-related health problems.[9] On the other hand, the Public Health Agency of Turkiye concluded that overweight causes more than 1 million deaths in the European Region each year.[10] According to the World Health Organization, obesity is among the main risk factors for cardiovascular diseases, diabetes, skeletal disorders, and some types of cancer.[11]

According to a study conducted by the OECD, the USA ranks first in terms of the distribution of obesity by country.[12] In addition, according to WHO data, adult obesity reached 650

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million worldwide in 2016.[13,14] According to the study by Kotseva and colleagues, the proportion of obese individuals in the total adult population is 13.1%; this rate was reported as 11.1% in men and 15.1% in women.[15] According to the results of UBS Research, obesity rates among adults were determined to be 39.8%, which covers approximately 93.3 million adults.[16,17] According to the 2012 obesity report, the obesity tendency was found to be more common in women with low income and education levels than in men. According to the same report, it was observed that the rate of obesity in men increased faster than in women.[18] Dietary habits are a critical factor affecting this energy balance.[19] The frequent consumption of high-calorie, low-nutrient foods, the spread of fast-food culture, the increasing popularity of processed foods-all these factors are major factors in the increasing prevalence of obesity.[20] In this context, a detailed examination of dietary habits is a critical step in developing effective strategies to combat obesity in individuals and societies.[21]

Adopting healthy eating habits, allocating time for regular physical activity, and developing personalized strategies tailored to the individual's lifestyle play a key role in obesity prevention.[22,23] A balanced diet provides the nutrients the body needs and is important for healthy weight management, and portion control is an effective strategy for obesity prevention.[24] Emotional eating has been associated with conditions such as stress and unhappiness, causing a tendency to overeat and triggering obesity. Finally, the combination of regular physical activity and healthy eating habits provides an effective combination for obesity prevention.[25]

Improving dietary habits can contribute to individuals adopting healthy lifestyles and preventing obesity. The aim of this article is to understand the effects of dietary habits on obesity in adult individuals and to highlight the information and relationships obtained to address this problem.

METHODS

Ethics

The study was carried out with the permission of Kırıkkale University Social and Human Sciences Researches Ethics Committe (Date: 21.02.2024, Decision No: 2024/E.234670). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Research Model

This study aims to examine the eating habits of adult individuals in detail at the level of different variables and to analyze these habits in terms of obesity and physical activity levels. In the study, a quantitative research method and a descriptive screening model, one of the general screening designs, were used for the purpose.

Research Group

The research group of this study consisted of 704 adult individuals in Kırıkkale province. A simple random sampling method was used in the study.

Data Collection

The Three-Factor Eating Questionnaire (TFEQ) is a questionnaire that measures the eating habits of individuals. It was translated into Turkish by Kıraç et al.[26] in 2015 under the name of "TFEQ" and its validity and reliability were proven, and its use in our country was ensured. The questionnaire consists of 18 items. The questionnaire measures the degree of consciously restricting their eating, the level of uncontrolled eating, and the degree of eating when they are emotional. The questionnaire also measures the level of sensitivity to hunger.

Data Analysis

Cronbach's alpha was analyzed to determine the reliability of the study. Since the data were distributed as normal binary, they met the prerequisites of parametric tests. For this reason, an independent sample t-test was used for pairwise group comparisons, and an ANOVA test was used for comparisons of three or more groups. In addition, in cases of a significant difference in ANOVA results, the Tukey post hoc test, one of the multiple comparison tests, was applied to determine which groups the difference was between. The following thresholds were used to determine the size of the effect of the relationships: <0.1=insignificant; 0.1-0.3=small; >0.3-0.5=moderate; >0.5-0.7=large; >0.7-0.9=very large; and >0.9=almost perfect. For statistical analysis, the Windows-based SPSS 22.0 statistical package was used. Results are presented as frequency distributions, mean values, and standard deviations in tables or text.

RESULTS

Statistical information about the demographic information of the participants in the groups is shown in (Table 1).

Table 1. Frequency and percentage distributions of the demographic characteristics of the participants

Variables		n	%
Total number of participants		704	100
Gender	Female	475	67.5
	Male	229	32.5
Place of residence	Urban	543	77.1
	Rural	161	22.9
Smoking	Yes	257	36.5
	No	447	63.5
Alcohol use	Yes	209	29.7
	No	495	70.3
Chronic illness	Yes	138	19.6
	No	566	80.4
Economic situation	Bad	117	16.6
	Middle good	398 189	56.5 26.8
Weekly physical activity	Nothing	179	25.4
	1 per week	88	12.5
	2 per week	123	17.5
	3 per week	121	17.2
	4 per week	101	14.3
	5 per week	92	13.1

According to the table above, 67.7% of the participants were female, and 77.1% lived in urban areas. In addition, 63.5% of the participants did not smoke, 70.3% did not drink alcohol, 80.4% did not have any chronic disease, 56.5% had a medium economic level, 17.5% did physical activity 2 days a week, and 17.2% did physical activity 3 days a week (Table 1).

When Table 2 is examined, it is seen that there is a significant difference between men and women in the emotional eating sub-dimension according to the three-factor nutrition questionnaire scores, and the effect size is low.

When Table 3 was examined, it was determined that there was a significant difference between participants living in urban and rural areas in the sub-dimensions of uncontrolled eating, emotional eating, and sensitivity to hunger according to the three-factor nutrition questionnaire scores of the place of residence variable. The largest effect size between the participants living in rural and urban areas was found to be in the emotional eating sub-dimension, while the smallest effect size was found in the uncontrolled eating sub-dimension.

When Table 4 was examined, it was determined that there was a significant difference in the sub-dimensions of uncontrolled eating, emotional eating, and sensitivity to hunger according to the three-factor nutrition questionnaire scores of smoking and non-smoking participants. It was observed that the highest effect level between smokers and non-smokers was in the sensitivity to hunger sub-dimension, and the lowest effect level was in the emotional eating sub-dimension.

When Table 5 was examined, it was determined that there was a significant difference between alcohol users and non-alcohol users in the sub-dimensions of uncontrolled eating, emotional eating, and sensitivity to hunger according to the three-factor nutrition questionnaire scores of the alcohol use variable. It was observed that the largest effect size between alcohol users and non-alcohol users was in the emotional eating sub-dimension, and the lowest effect size was in the uncontrolled eating sub-dimension.

Table 2. T-test results of TFEQ scores according to gender

Dimension	Female (n=475) Mean±SD	Male (n=229) Mean±SD	t	Cohen's d	p
Uncontrolled eating	12.07±2.08	11.70±2.15	2.110	0.18	0.330
Emotional eating	8.13±2.85	9.40±2.38	-5.859	0.49	0.001*
Conscious eating	17.68±3.16	17.48±3.36	.752	0.07	0.453
Hunger sensitivity	11.30±3.22	11.21±3.41	.322	0.03	0.743

TFEQ: Three-factor eating questionnaire, SD: Standart deviation, *p<0.001

Table 3. T-test results of TFEQ scores according to place of residence

Dimension	Residence	n	Mean	SD	t	Cohen's d	p
Uncontrolled eating	Urban	543	12.11	2.04	3.282	0.31	0.001*
	Rural	161	11.45	2.27			
Emotional eating	Urban	543	9.06	2.54	8.958	0.84	0.001*
	Rural	161	6.82	2.84			
Conscious eating	Urban	543	17.72	3.16	1.518	0.14	0.113
	Rural	161	17.26	3.42			
Hunger sensitivity	Urban	543	11.78	3.11	7.714	0.69	0.001*
	Rural	161	9.59	3.31			

TFEQ: Three-factor eating questionnaire, *p<0.001

Table 4. T-test results of TFEQ scores according to smoking status

Dimension	Cigarette use	n	Mean	SD	t	Cohen's d	p
Uncontrolled eating	Yes	292	11.62	2.11	-3.572	0.28	0.001*
	No	412	12.19	2.09			
Emotional eating	Yes	292	8.15	2.91	-3.178	0.25	0.001*
	No	412	8.83	2.66			
Conscious eating	Yes	292	17.28	3.20	-2.365	0.19	0.018
	No	412	17.86	3.24			
Hunger sensitivity	Yes	292	10.48	3.49	-5.420	0.42	0.001*
	No	412	11.85	3,02			

TFEQ: Three-factor eating questionnaire, *p<0.001

Table 5. T-test results of TFEQ scores according to alcohol use status

Dimension	Alcohol use	n	Mean	SD	t	Cohen's d	p
Uncontrolled eating	Yes	209	11.45	2.17	-4.056	0.35	0.001*
	No	495	12.17	2.06			
Emotional eating	Yes	209	7.44	2.87	-6.873	0.58	0.001*
	No	495	9.02	2.61			
Conscious eating	Yes	209	17.14	3.14	-2.551	0.22	0.010
	No	495	17.82	3.26			
Hunger sensitivity	Yes	209	10.17	3.50	-5.667	0.48	0.001*
	No	495	11.75	3.09			

TFEQ: Three-factor eating questionnaire, *p<0.001

When Table 6 is examined, it is determined that there is a significant difference between the participants with and without chronic disease in the sub-dimensions of emotional eating, conscious eating, and sensitivity to hunger according to the three-factor nutrition questionnaire scores of the chronic disease variable. It was observed that the largest effect size between the participants with and without chronic disease was in the emotional eating sub-dimension, and the lowest effect size was in the conscious eating sub-dimension.

When Table 7 was examined, it was determined that there was a significant difference between the participants in the sub-dimensions of uncontrolled eating and conscious eating according to the three-factor nutrition questionnaire scores of the economic status variable. According to the ANOVA results, it was determined in both sub-dimensions that the eating habits scores of the participants with good and medium economic status were high, while the eating habits scores of the participants with poor economic status were low. It was observed that there was no significant difference in the emotional eating and hunger tolerance sub-dimensions.

When Table 8 was examined, it was determined that there was a significant difference in the sub-dimensions of uncontrolled eating, conscious eating, and sensitivity to hunger according to the three-factor nutrition questionnaire scores of the weekly physical activity variable. According to the ANOVA results, it was determined that the scores of those who performed physical activity 5 times a week, 4 times a week, and 3 times a week were high, while the scores of those who performed physical activity 2 times a week, 1 time a week, and never a week were low. There was no significant difference in the emotional eating sub-dimension.

Table 6. T-test results of TFEQ scores according to chronic disease status

Dimension	Chronic illness	n	Mean	SD	t	Cohen's d	p
Uncontrolled eating	Yes	138	11.53	2.38	-2.437	0.24	0.008
	No	566	12.06	2.04			
Emotional eating	Yes	138	6.99	2.89	-7.188	0.70	0.001*
	No	566	8.92	2.62			
Conscious eating	Yes	138	16.84	3.49	-2.996	0.30	0.001*
	No	566	17.81	3.15			
Hunger sensitivity	Yes	138	9.50	3.44	-6.900	0.68	0.001*
	No	566	11.72	3.11			

TFEQ: Three-factor eating questionnaire, SD: Standart deviation, *p<0.001

Table 7. ANOVA results of TFEQ scores according to economic status

Dimension	Economic situation	n	Mean	SD	F	p	Tukey
Uncontrolled eating	Bad[1]	117	11.24	2.13	8.160	0.001*	3=2>1
	Middle[2]	398	12.09	2.00			
	Good[3]	189	12.12	2.27			
Emotional eating	Bad[1]	117	6.49	2.67	49.823	0.393	-
	Middle[2]	398	8.70	2.60			
	Good[3]	189	9.50	2.59			
Conscious eating	Bad[1]	117	16.90	3.42	3.708	0.001*	3=2>1
	Middle[2]	398	17.82	3.11			
	Good[3]	189	17.63	3.33			
Hunger sensitivity	Bad[1]	117	9.36	3.38	28.954	0.716	-
	Middle[2]	398	11.45	3.17			
	Good[3]	189	12.13	3.03			

TFEQ: Three-factor eating questionnaire, SD: Standart deviation, *p<0.001

Table 8. ANOVA results of TFEQ scores according to weekly physical activity status

Dimension	Physical activity status	n	Mean	SD	F	p	Tukey
Uncontrolled eating	Nothing[1]	169	11.72	2.30	2.218	0.001*	6=5=4>3=2=1
	1 per week[2]	82	11.54	2.17			
	2 per week[3]	129	11.90	1.85			
	3 per week[4]	131	12.32	2.04			
	4 per week[5]	111	12.05	1.92			
	5 per week[6]	82	12.25	2.34			
Emotional eating	Nothing[1]	169	7.25	3.13	11.569	0.393	-
	1 per week[2]	82	8.60	2.69			
	2 per week[3]	129	8.80	2.52			
	3 per week[4]	131	8.97	2.58			
	4 per week[5]	111	9.46	2.22			
	5 per week[6]	82	8.86	2.59			
Conscious eating	Nothing[1]	169	16.53	3.43	0.766	0.001*	6=5=4>3=2=1
	1 per week[2]	82	16.21	3.26			
	2 per week[3]	129	16.41	2.63			
	3 per week[4]	131	18.47	3.12			
	4 per week[5]	111	18.73	3.20			
	5 per week[6]	82	18.64	3.86			
Hunger sensitivity	Nothing[1]	169	10.15	3.88	7.346	0.001*	6=5=4>3=2=1
	1 per week[2]	82	10.05	3.19			
	2 per week[3]	129	10.40	3.16			
	3 per week[4]	131	11.69	2.88			
	4 per week[5]	111	12.36	2.45			
	5 per week[6]	82	12.55	3.27			

TFEQ: Three-factor eating questionnaire, SD: Standart deviation, *p<0.001

DISCUSSION

The aim of this study is to examine the dietary habits of adult individuals in detail at the level of different variables and to analyze these habits in depth in terms of obesity and physical activity levels. When the results obtained from the study were analyzed, it was determined that the majority of the participants were female, lived in urban areas, did not smoke or drink alcohol, and did not have chronic diseases. It was determined that the individuals with moderate economic status and weekly physical activity rates were scattered and that the individuals who mostly performed physical activity 2 or 3 days a week were included in the study.

According to the three-factor nutrition questionnaire scores between men and women, it was observed that there was a significant difference between genders in the emotional eating sub-dimension, and the scores of men were higher than the scores of female participants. It is thought that men tend to eat more than women due to the fact that they share their emotional state less than women. Düz, Taşkıran, and Sadık[27] found that female basketball players developed uncontrolled eating behavior due to unbalanced nutrition in their study. Tayfun et al.[28] found that there was no difference between genders in the emotional eating and uncontrolled eating sub-dimensions of eating habits. Seremet Kürklü et al.[29] reported that the uncontrolled eating and emotional eating scores of females were higher than those of males in a study conducted on adolescents. In the study conducted by İskender and Yıldırım[30] it was determined that women had higher values of uncontrolled eating behavior than men. It was observed that there were studies in the literature that were not similar to our study.

According to the three-factor nutrition questionnaire scores of the variables of place of residence, smoking and alcohol use, it was determined that there was a significant difference between the participants living in urban and rural areas in the sub-dimensions of uncontrolled eating, emotional eating, and sensitivity to hunger, and between smokers and alcohol users and non-users. According to the place of residence, it was determined that those living in urban areas and those who said no to smoking and alcohol use had low scores in the sub-dimensions of uncontrolled eating and emotional eating and in favor of them, and those who said no to smoking and alcohol use had low scores in the sub-dimensions of sensitivity to hunger but against them. Those who lived in rural areas and smoked and drank alcohol had high scores in the sub-dimensions of uncontrolled eating and emotional eating, and high scores in the sub-dimensions of sensitivity to hunger and favorable scores. No significant difference was found in the conscious eating sub-dimension. It is thought that those who do not smoke and drink alcohol have high awareness and consciousness about eating habits. Since individuals living in cities have easier access to information, it is thought that they develop awareness in order to acquire nutritional habits and are informed about nutrition. Acemioğlu and Doğan[31] stated that there was no difference in attitudes towards healthy eating according to the place of residence variable in their study for science teachers. In Çakar and Arslan's[32] study on emotional nutrition in 2023, they stated that place of residence, smoking and alcohol use were effective on eating behavior.

According to the three-factor nutrition questionnaire scores of the chronic disease variable, it was determined that there was a significant difference between the participants with and without chronic disease in the sub-dimensions of emotional eating, conscious eating and sensitivity to hunger. This difference was found to be high in favor of those who said yes to conscious eating and sensitivity to hunger in those without chronic disease. In the emotional eating sub-dimension, it was found to be high in favor of those who said yes. It is thought that the eating habits of individuals without chronic diseases are also regular and that this order contributes to them not to develop chronic diseases. Bolayır et al.[33] evaluated the differences that cause obesity and stated that the most important factors that cause obesity are eating habits, insufficient physical activity, and lack of awareness of healthy eating. In the study conducted by Tuncel et al.,[34] the most important factors causing obesity are nutrition and physical inactivity. Acemioğlu and Doğan[31] stated that there was no difference in attitudes towards healthy eating according to the variable of having a chronic disease.

According to the three-factor nutrition questionnaire scores of the economic status variable, it was determined that there was a significant difference between the participants in the sub-dimensions of uncontrolled eating and conscious eating. In both sub-dimensions, it was determined that the nutritional habit results of the participants with good and medium economic status were high, while the nutritional habit scores of the participants with poor economic status were low. It is thought that individuals with good economic status can make choices according to their awareness status because they have many opportunities in the sub-dimensions of uncontrolled eating and conscious eating on behalf of eating habits. Taşçene and Koçoğlu[35] found that balanced nutrition did not differ according to economic status in their study on eating habits. In the study conducted by İskender et al.,[36] it was concluded that the balanced nutrition status of university students did not differ according to economic status. In the study conducted by Sonğur et al.[37] on the nutritional status of patients receiving health services, it was seen that healthy eating status does not differ according to economic factors. Acemioğlu and Doğan,[31] in their study for science teachers, stated that the monthly income level of families did not make a difference in their attitudes towards healthy nutrition. It was seen that these studies did not overlap with our research. In their study on eating habits in 2020, Gül and Gül[38] found that the nutritional problems of individuals with low economic levels increased.

It was determined that there was a significant difference in the sub-dimensions of uncontrolled eating, conscious eating, and sensitivity to hunger according to the three-factor nutrition questionnaire scores of the weekly physical activity variable. It can be concluded that those who do more physical activity are more conscious of nutrition, have higher levels of awareness, and according to these results, those who do more activity are attentive to nutrition. This situation can also be associated with obesity. Since individuals who do more activity can also develop sensitivity to hunger, it is thought

that they are far away from obesity. In the study, it was concluded that individuals who show sensitivity to hunger can make healthy and conscious dietary choices, so they may be less likely to develop obesity. Kıymaz and Süel,[39] in their study on physical activity and nutritional habits of university students in 2024, stated that individuals who do more physical activity have more regular eating habits. In a study conducted by Dinç et al.[40] in 2017 on the nutritional habits of individuals who exercise, it was concluded that individuals who engage in physical activity have a more balanced diet. In the study conducted by Güldal et al.[41] on the students of the faculty of sports sciences in 2023, it was determined that the nutritional habits of individuals who regularly engage in physical activity are at a good level. The results of the study are similar to ours. Cheng et al.,[42] in their study on eating and physical activity behaviors, found that weight-related self-stigma was significantly associated with both healthy eating and physical activity behaviors.

CONCLUSION

This study reveals that dietary habits are influenced by variables such as gender, place of residence, smoking and alcohol use, chronic disease, and economic status, and that these habits are linked to obesity and physical activity levels. According to the findings of the study, it was concluded that these variables have significant effects on nutrition behaviors. In particular, lifestyle factors such as healthy eating and regular physical activity were found to play an important role in reducing obesity. It is important to organize nutrition education and awareness programs, especially for economically disadvantaged groups. These groups should be provided with support and resources to develop healthy eating habits and regular physical activity. For these reasons, it is inevitable that health policies and individual health programs should take these factors into account. Taking these important factors into account will increase the effectiveness of health services and improve the overall health of the population.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was carried out with the permission of Kırıkkale University Social and Human Sciences Researches Ethics Committe (Date: 21.02.2024, Decision No: 2024/E.234670).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authours have no conflicts of interest to declare.

Financial Disclosure

This study has not received any financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1465719
J Health Sci Med. 2024;7(3):308-313

Retrospective analysis of the endovascular and surgical treatment outcomes in 105 patients with cerebral arteriovenous malformation

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Cite this article as: Oğur T, Belen AD, Dağlıoğlu E, et al. Retrospective analysis of the endovascular and surgical treatment outcomes in 105 patients with cerebral arteriovenous malformation. *J Health Sci Med.* 2024;7(3):308-313.

Received: 15.04.2024 ◆ **Accepted**: 11.05.2024 ◆ **Published**: 27.05.2024

ABSTRACT

Aims: We aimed to compare the short-term follow-up outcomes of treatment with liquid embolization agents in 105 patients with low- and medium-grade arteriovenous malformation (AVM) having supra- or infratentorial localization and its reliability and efficacy.

Methods: This retrospective study assessed patients diagnosed with grade I, II, III, IV, and V infratentorial AVM according to the Spetzler–Martin grading system who received endovascular treatment and underwent surgical resection. The pre-treatment, post-treatment, preoperative, postoperative, and follow-up data and the electronic radiograph findings, epicrisis reports, and clinical follow-up reports were recorded and examined.

Results: AVM was detected in 105 patients, who underwent 132 endovascular treatment sessions in total. Of the 105 patients, 47 were fed with a single venous system; 37 with two venous systems; and 21 with three or more venous systems. The mean follow-up duration was 28 months, and no patient presented with re-hemorrhage. Some of the complications associated with embolization were hemiparesis/hemiplegia, hemihypesthesia, hemorrhage and hematoma, vision disorders and alar defects, cranial nerve paralysis, and aphasia/dysphasia. Meanwhile, seven patients died after treatment.

Conclusion: AVM treatment generally includes usage of gamma knife, endovascular treatment, surgical resection, or the combination of such treatments. If surgical resection is performed, a complete and absolute outcome can be achieved. However, complete treatment can be rarely achieved with endovascular therapy alone. Higher morbidity and mortality rates were observed in patients with hemorrhage than in those without.

Keywords: Arteriovenous malformation, endovascular treatment, surgery, complication

INTRODUCTION

Cerebrovascular malformations (CVMs) comprise a heterogeneous group of disorders, including vascular malformations observed in the brain, associated with a wide spectrum of behaviors. Some disorders (i.e., capillary malformations) might be asymptomatic and can be detected incidentally during imaging. CVMs, such as arteriovenous malformation (AVM) and cavernous angioma, might cause unexpected bleeding without any prior triggering symptom.[1]

AVM is an irregular angiogenesis characterized by the formation of a direct shunt between the artery and vein, and such a lesion can be observed in up to 0.05% of the population. The annual incidence rates of hemorrhage increase in parallel with age, localization in the deep brain, and deep venous drainage. The annual risk of hemorrhage varies is 1%-35% in patients meeting all these three criteria.[1]

The treatment options are transluminal embolization, surgery, stereotaxic radiosurgery, and the combination of such treatments (multimodal surgery), and the best option is determined based on the patient condition.[2,3]

Complete embolization of a lesion is directly associated with the lesion size, and lesions may have one or two feeders of a diameter <3 cm. In a patient who will undergo surgery, embolization of the lesion before the procedure decreases the risk of surgery and hemorrhage. Moreover, if there is no pressure effect on the lesions with total or gross total embolization, surgery may not be required.[2]

Thus, in the present study, we aimed to examine the short-term follow-up outcomes of 105 patients who have low-or medium-grade AVM with supra-or infratentorial localization and have been treated with liquid embolization agents in 2011-2016. Moreover, the reliability and efficacy of the treatment was assessed.

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METHODS

The study was carried out with the permission of Ankara Numune Training and Research Hospital Clinical Researches Ethics Committee (Date: 12.04.2017, Decision No: 1368). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective study evaluated patients who were diagnosed with grade I, II, III, IV, and V infratentorial AVM according to the Spetzler-Martin grading system and received endovascular treatment and underwent surgical resection. The pre-treatment, post-treatment, preoperative, postoperative, and follow-up data and the electronic radiograph findings, epicrisis reports, and clinical follow-up reports were recorded and examined.

Patient Information

In the present study, patients with AVM who presented with headache, seizure, and hemorrhage and those incidentally diagnosed with cerebral AVM between 2011 and 2016 were included. No age or gender exclusion criterion was applied.

The patients presented with symptomatic and asymptomatic AVM with supratentorial or infratentorial localization. We conducted treatment with liquid embolization agent+surgical resection via the endovascular path in the interventional radiology unit.

In all patients, prior to treatment, the digital subtraction angiography (DSA) method was used for anterior, posterior cerebral circulation and bilateral external carotid artery (ECA) imaging, and the 3D angiographs of the AVM were obtained for the measurement of the nidus. The other treatment alternatives were discussed with the neurosurgery and radiology departments council before the treatment. The patient and their relatives are informed about the treatment options and risks, as well as the treatment recommended by our council. The treatment preferred by the patient and their relatives is implemented.

Treatment Information and Informed Consent

The patients who were candidates for endovascular treatment and their relatives were informed about the natural course of AVM as well as the advantages, disadvantages, benefits, and complications of endovascular and surgical treatments. Then, a written informed consent was obtained.

The fundamental clinical examination results and the platelet count, serum creatinine level, and hemoglobin values of the patients were examined prior to the procedure.

Medications

All patients underwent the treatment procedure under general anesthesia. The medications suitable for general anesthesia were used by the anesthetist team in accordance with the standard protocols of the hospital. In all patients, the bolus dosage was intravenously applied to ensure 2-2.5 folds of the basal-bolus heparin international normalized ratio of the minimum and maximum units at 3000 and 6000, respectively. The hourly treatment dose was 500–1000 units. At the end of the procedure, the use of heparin was reversed to prevent hemorrhage.

Equipment

The transfemoral path was used in all patients. Cerebral arteriogram was first conducted. Then, based on the localization of AVM, the guide sheath and catheter were placed into the carotid or vertebral artery. Then, with the use of the micro-catheters, the AVM feeder was catheterized. In relation to the other feeders, the catheterization was performed based on the passage feeder condition. A suitable wire was used to better visualize the flow-directed microcatheters and prevent the formation of a gap due to a sudden stop. After successfully completing the catheterization, the micro-catheters were rinsed with SF, and based on the gaps inside, their interiors were filled using dimethyl sulfoxide. Then, the injection of ethylene vinyl alcohol (EVOH) was initiated, which was applied slowly and periodically via manual injection for a duration of 20-40 min. The proximal n-butyl cyanoacrylate was applied to prevent reflux in the large feeders of large aneurysms.

The control angiographs were obtained right after completing the procedure, and the evaluations were made based on the AVM obliteration levels and possible complications, such as parent artery occlusion, vasospasm, thromboembolism, EVOH reflux, and recurrent hemorrhage (Figure). Unenhanced computed tomography (CT) imaging was performed within the first 3 h after the procedure to assess for hemorrhage.

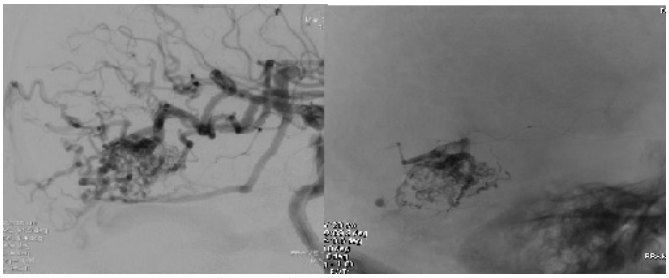

Figure. Preoperative and control angiographs

RESULTS

AVM was detected in 105 patients, who underwent a total of 132 endovascular treatment sessions. Subarachnoid hemorrhage and subdural and/or parenchymal hematoma were observed in 32 of 105 patients with AVM. The patients were aged between 11 and 69 years, with a mean age of 37 years. In addition, minor symptoms, such as severe seizure and headache, were observed, and 23 patients had neurological deficits and low Glasgow coma scale (GCS) scores during admission. Twenty-seven patients had AVM with non-cortical deep localization. Eleven patients presented with infratentorial localization. In 11 patients, cerebral aneurysm was observed on the feeder veins or another localization. Twenty-two patients had AVM with occipital localization; 15 with parietal localization; 11 with frontal localization; 10 with temporal localization; 15 with tentorial localization; seven with intraventricular localization; six with Sylvian localization; four with frontobasal localization; three with interhemispheric localization; and one with orbital localization. Using the Spetzler-Martin grading system, six patients presented with grade I AVM; 33 with grade II AVM; 29 with grade 3 AVM; 18 with grade 4 AVM; 8 with grade 5 AVM; and 11 with infratentorial AMV. Moreover, 47 patients were fed with a single venous system; 37 with two venous systems; and 21 with three or more venous systems.

In 60 patients, surgical resection was performed during embolization. Total resection was achieved during surgery in all cases. The postoperative residual filling was followed only in three cases. Two patients underwent re-surgery, and re-embolization was successfully achieved in one case. Three patients underwent embolization after gamma knife; in 19 patients, gamma knife was recommended as a complementary treatment after endovascular treatment. The mean follow-up duration was 28 months, and none of the patients presented with re-hemorrhage during the follow-up.

The major complications observed in the cases were divided into two groups: secondary to embolization and secondary to surgery. Patients with neurological deficit or low GCS score before embolization or surgery were excluded. However, notably, a significant proportion of patients in this group developed complications (Table 1).

Table 1. Complications observed in patients with arteriovenous malformation

No	Type	Presentation	Localization	Feeder	Postoperative complications	Grade
1	30	Headache	Left occipitotentorial AVM	Left MCA distal branches	Postoperative visual field defect	2
2	34	Headache	Right occipitotentorial AVM	Right MCA inferior trunk+PCA	Visual field defect	4
3	42	Headache	Left occipital AVM	Left PCA	Visual field defect	3
4	30	Headache	Left occipital AVM	AICA, Left SSA, PICA	Postoperative hemorrhage, GCS score of 6	3
5	43	Headache	Left frontal interhemispheric AVM	Left MCA	Aphasia	3
6	19	SAH Headache	Right occipital AVM	Right MCA, PCA, ECA	Visual field defect	4
7	24	Treatment after the gamma knife	Left cerebellar AVM	Left PCA, PICA, AICA	Nistagmus, ataxia	3
8	37	Embolized AVM	Residual left occipital AVM	Left MCA, PCA	Visual field defect, aphasia	3
9	21	Loss of consciousness, parietal hematoma	Right occipitotentorial AVM	Right PCA	Paralysis	4
10	39	Headache	Left frontal AVM	Left MCA	Paresis	2
11	38	SAK Intraventricular hemorrhage	Left ventricular AVM	Left MCA, choroidal	Paralysis, aphasia, seizure	3
12	25	Headache	Right parietal AVM	Right MCA, ACA	Paresis	3
13	48	Headache	Left temporal AVM	Left MCA, PCA	Aphasia	5

MCA: Middle cerebral artery, PCA: Posterior cerebral artery, ECA: External carotid artery

The complications associated with embolization were hemiparesis/hemiplegia, hemihypesthesia, hemorrhage and hematoma, vision field defects, cranial nerve paralysis, and aphasia/dysphasia (Table 2 and Table 3). Hemorrhage was observed during 6 of 126 sessions of endovascular AVM embolization, and all patients immediately underwent surgery. Despite such treatment, three of these patients died. These cases were considered as mortality associated with endovascular treatment. In three hemorrhagic cases, complete resection could have been achieved during post-embolization AVM surgery; except for one patient, two patients were discharged without any major sequela. Of 105 patients, 8 developed major complications, such as hemiplegia, cerebellar ataxia, and aphasia, and five patients had minor complications, including visual field defect, nystagmus, and hemihypesthesia. Five of the eight patients had major complications with a modified rankin scale score of ≥3.

Table 2. Embolization and morbidity/mortality rates

Group	Total	Morbidity	Mortality
100-91%	34	6	1
90-76%	18	3	1
<75%	8	2	5

Table 3. Arteriovenous malformation cases: complication rates based on the Spetzler–Martin grading system

Grade	Complication/Total	%
2	2 (33)	6
3	6 (29)	20
4	3 (18)	16
5	1 (8)	12
Infratentorial	1 (11)	9

During treatment, the complications associated with endovascular therapy was observed in three patients (Table 4). Reflux to the left A2 was observed in one case because the endovascular filling material could not be observed, and an immediate reflux to the posterior choroidal artery was found in one patient after the embolization of the posterior cerebral artery (PCA) feeder. In two cases, the reflux occurred because the catheter was removed using a snare since the detachable catheters did not break.

Table 4. Morbidity and mortality analysis of patients with AVM using the feeder vascular branch group (i.e., MCA or ACA or PCA) and the single-branch group

Feeder	Total	Morbidity	Mortality
Single system	47	5	4
Two systems	37	5	3
Multiple feeders	21	5	0

AVM: Arteriovenous malformation, MCA: Middle cerebral artery, PCA: Posterior cerebral artery

A total of seven patients died (Table 5 and Table 6). Hemorrhage was observed in five cases, whereas the GCS scores of three patients were lower than 14. Three patients died due to complications that developed after endovascular treatment, one patient due to re-hemorrhage during hospital follow-up, and three patients due to complications that developed after surgery. Two of these cases involved infratentorial AMV, whereas the mean Spetzler-Martin grade of the remaining five patients was 3. One of these patients had cerebellar localization, one with 4th ventricle localization, two with parietal localization, two with Sylvian location, and one with orbital localization. The mortality rate was high particularly in patients with hemorrhage.

Table 5. Characteristics of the seven patients with AVM who died

Patient	Age	Sex	Presentation	Localization	Feeder	Excision	Grade
1	63	M	Hemiparesis, left parietal hematoma	Left occipitoparietal AVM	Left ACA PCA	-	3
2	39	M	Headache, visual field deficit	Right Sylvian AVM	Right MCA	+	3
3	25	M	Headache	Right Sylvian AVM	Right MCA	+	4
4	52	M	Ptosis, headache, hemorrhage, GCS 13	Left orbital AVM	Right ophthalmic AVM	+	2
5	55	M	Visual field defect, imbalance	AVM in 4th ventricle	AICA, SSA	+	-
6	56	M	SAH, GCS 8	Left cerebellar AVM fed by artery AVM	Left AICA, SSA	+	-
7	69	M	Previous parenchymal hemorrhage, headache	Left frontotemporal AVM	Right MCA	+	2

AVM: Arteriovenous malformation, PCA: Posterior cerebral artery, **MCA: Middle cerebral artery, AICA: Anterior inferior serebellar arter GCS: Glasgow Coma Scale**

Table 6. Morbidity rates of patients with arteriovenous malformation based on the Spetzler-Martin grading system

Grade	Deceased/Total	%
1	0 (6)	0
2	2 (33)	6
3	2 (29)	7
4	1 (18)	5
5	0 (8)	0
Infratentorial	2 (11)	18

DISCUSSION

Cerebral AVMs are lesions that are extremely challenging to treat. The radiological anatomy plays an important role in the treatment of such lesions. For both endovascular and surgical resections, knowledge about the anatomy increases the rate of successful surgeries and decreases the risk of complications. Another important point is the difference in the normal vascular structures arising from the AVM feeder. During surgical and endovascular treatments, these normal structures arising from the feeders should be protected and not undergo embolization.

The diameter of the AVM nidus is also an important parameter for successful surgical and endovascular interventions. The success rates, particularly in AVM cases with ≤3 cm diameter, significantly differ in the literature.[4] 3D DSA is more sensitive in measuring the diameter of the AVM nidus than magnetic resonance imaging angiography or CT angiography.[5]

The Spetzler-Martin grading system is a widely used method. However, the Spetzler- Ponce and Lawton grading has replaced the use of such system in recent years.[6,7] The evaluation of clinical success and mortality is extremely important particularly after surgical resection.[8-12]

The clinical outcomes significantly differ in hemorrhagic cases.[13,14] The mortality rate was 1% during the endovascular embolization of cerebral AVM. The hemorrhagic complications might be observed in 2%-5% of the cases. The morbidity rate varied between 10% and 14%.[15-21]

In addition, anomalies in adjacent cerebral tissues, aneurysms on the feeding artery, and presence of any pre-treatment hemorrhage and/or hematoma are extremely important for the planning and success of treatment. In particular, patients with aneurysms on the feeding artery are at risk of hemorrhage during feeder catheterization; thus, extreme caution must be exercised. Another important point is that the feeding arteries arise from different vascular structures; for example, the risk of hemorrhage during an endovascular or surgical intervention is high in patients with AVM who underwent vascularization from the middle cerebral artery (MCA), anterior cerebral artery, PCA, and even ECA branches and have multiple feeders; in comparison, the risk is relatively lower in patients with AVM who were fed with a single venous system (particularly the MCA branches). Among the patients with AVM who underwent surgery in our clinic, the mortality and morbidity rates were lower in those fed with a single pedicle than in those fed with two or more feeders.

The relationship between the ectasias observed in the venous system and venous sinuses plays an important role particularly in surgical planning owing to the use of flux only in the venous system and risk of reflux during the endovascular treatment. The presence of veins before the surgical corridor is a significant challenge in planning any AVM surgery, and it should be projected at the planning phase. Premature occlusion of the venous system during embolization increases the risk of preoperative hemorrhage. Similarly, clipping the veins during an AVM resection by considering them as arteries may cause aneurysm or hemorrhage in the AVM nidus. Under any condition, one must pay attention in preventing the development of reflux in these veins during endovascular treatment, and all the feeders must be closed without occlusion. During surgical interventions, the final grade of the nidus feeder resection is to clip the feeding veins and to rapidly excise the AVM.

The success of using endovascular embolization agents may be directly associated with the morphological anatomy. In particular, low- and high-density EVOH polymers are widely used, and it is extremely important to properly use these agents. If embolization is initiated at the point of the feeding artery adjacent to the vein, selecting a high-density embolization agent would decrease the risk of reflux. Conversely, for points far from the vein, selection of a low-density agent might result in a more diffuse and successful embolization with better propagation. Similarly, successful embolization can be achieved using high density embolization agents in cases of high-flux AVM, and the risk of reflux might be prevented almost completely with the use of low-density agents.

In AVM cases, recurrence is widely observed in patients treated using only the endovascular method, even if radical surgery is successful. It is extremely difficult to recommend embolization as a primary treatment method. It is more appropriate to consider such a method auxiliary to surgery in AVM cases, particularly in the resectable areas.

For cerebral AVMs, embolization during surgery is extremely useful in localizing the lesion because the embolization agent is black, which is why it can be distinguished from the brain tissue; also, it limits the requirement of using neuronavigation. In surgeries performed by assuming that the adjacent cerebral vascular structures are protected, the gross excision of the vascular structures that are full of embolization agent indicates the excision of the nidus. In relation to this, the exception is maybe to partially leave the nidus as residual particularly in diffuse AVMs. The complexity of distinguishing the artery from the vein during surgery can be eliminated. In addition, particularly for cases with an embolization rate of 95% or higher, the risk of hemorrhage during EVM excision is almost completely eliminated, and the requirement of using Doppler during surgery is partially overcome. In other words, excision may be easier to achieve in such case than in an avascular meningioma case.

The success rate decreases in multi-feeder AVM cases and increases in single-feeder AVMs. One of the reasons is that endovascular treatment is assumed to be difficult since the multifeeder AVMs are generally large and these types of AVMs generally have complex vascular structures. In cases in which complete surgical resection is challenging, the use of endovascular treatment or the combination of endovascular treatment and gamma knife radiosurgery can be an option.

In addition, if AVM treatment has been initiated using any method, then the treatment must be completed. In the A Randomized Trial of Unruptured Brain Arteriovenous Malformations study, the risk of hemorrhage increases if the procedure is not completed[22]. If surgical resection is not considered for treatment, either embolization or the gamma knife method or the combination of both can be the other options, which is based on what method suits the condition of the patient.

Distinguishing hemorrhagic from non-hemorrhagic AVM is exremely important for the selection of treatment parameters. In particular, for hemorrhagic cases, both high risk for preoperative re-hemorrhage and the advantage of easily performing dissection in hemorrhagic cases validate the need for surgical intervention. Considering the findings of the present study showing that four of six patients who presented with hemorrhage prior to surgery have been admitted due to re-hemorrhage, those who had hemorrhage prior to surgery are at higher risk for re-hemorrhage.

Patients with infratentorial AVM should be examined separately from those with supratentorial AMV. Thus, the Spetzler–Martin grading was not applied to these patients in our series. Young patients with infratentorial AVM are at high risk of hemorrhage (5–6 times higher than in supratentorial cases), and this result indicates that the treatment of these patients must be immediately started.[23] Hemorrhage was observed in the second session after the first embolization session of a patient with cerebellar AVM who was admitted to our clinic due to hemorrhage. In such cases, caution must be observed. Moreover, patients must be closely monitored for hydrocephaly due to the posterior fossa localization. Watchful waiting or even prophylactic ventriculostomy might be preferred for patients who underwent embolization. In our clinical series, the patient with AVM in the 4th ventricle (Patient 80) died despite cautious monitoring after endovascular treatment because of cardiac arrest due to hydrocephaly. Although ventriculostomy was immediately performed, the clinical condition of the patient did not change.

An interesting relationship was observed between the embolization rate and surgical success and risk in AVM cases. In our series, the embolization rates in patients with AVM who underwent endovascular obliteration or surgical resection after the session(s) were divided into three groups: ≤75%, between 75 and 90%, and ≥90%. Eight patients presented with an embolization rate of 75% or lower; 18 with an embolization rate between 75 and 90%; and 34 with an embolization rate of 90% or higher. The complication rates of the groups are presented in Table 2.

CONCLUSION

The treatment of AVM is extremely complex, and the treatment options are generally gamma knife, endovascular treatment, surgical resection, or the combination of such treatments. In particular, when surgical resection can be performed, an absolute and complete outcome can be achieved. By contrast, complete treatment with endovascular therapy alone can be rarely achieved. Endovascular treatment decreases the risks associated with surgical resection. However, such procedure results in higher mortality and morbidity rates in hemorrhagic than in non-hemorrhagic patients according to the Spetzler–Martin grading system.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ankara Numune Training and Research Hospital Clinical Researches Ethics Committee (Date: 12.04.2017, Decision No: 1368).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1454820
J Health Sci Med. 2024;7(3):314-320

Protective effects of curcumin and quercetin in studies on cancer: a meta-analysis study

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Cite this article as: Altınkaynak Y, Akcan Altınkaynak B. Protective effects of curcumin and quercetin in studies on cancer: a meta-analysis study. *J Health Sci Med.* 2024;7(3):314-320.

Received: 18.03.2024 ◆ **Accepted**: 11.05.2024 ◆ **Published**: 27.05.2024

ABSTRACT

Aims: Polyphenolic chemicals, such as quercetin and curcumin have anti-cancer properties due to their antioxidant and anti-inflammatory properties. Quercetin and curcumin aids in detoxification by boosting enzyme function and eliminating free radicals. We aimed to conduct a detailed meta-analysis of research articles reporting the protective effects of curcumin and quercetin in cancer studies.

Methods: The study was selected all studies over time carried out to date within the framework of our concept ,using various medical subject headings and databases like Elsevier, National Library of Frontiers, ResearchGate, Scopus Medicine, and Google Scholar. PRISMA guidelines was performed. The data management system played a significant role in locating and evaluating relevant articles, ensuring the accuracy and precision of the findings.

Results: From a total of 85 articles accessed in this analysis, 4 studies on quercetin and 3 studies on curcumin were included. The analyzed studies show that quercetin and curcumin have anti-cancer benefits through various cellular pathways. Quercetin inhibits Twist in breast cancer cells, while curcumin reduces Akt/mTOR cellular signaling, enhances Bax expression, and triggers cell death. It also prevents cell growth in human lung cancer cells and bladder cancer. Curcumin control reactive oxygen species levels, inhibit cancer cell proliferation, and stimulate apoptotic pathways. They also influence cancer development by altering cellular signaling pathways and affecting non-coding RNAs.

Conclusion: Our meta-analysis reports that quercetin and curcumin have the potential to be used in the treatment and prevention of cancer, it may be useful to investigate their synergistic effects.

Keywords: Antioxidants, cancer, curcumin, functional foods, quercetin

INTRODUCTION

Polyphenols are natural chemicals present in plants, recognized for their antioxidant characteristics and possible health advantages. They are present in fruits, vegetables, tea, coffee, red wine, and plant-based diets.[1] They are a diverse category of natural bioactive phytochemicals that are found extensively distributed. These are characterized by aromatic rings attached to hydroxyl groups in their structure.[2] Polyphenols have demonstrated supplementary advantageous impacts on human health, in addition to their antioxidant action.[3] Epidemiological studies have shown that consuming dietary polyphenols can help protect against various types of cancer, as well as acute and serious ailments like cardiovascular diseases and osteoporosis, neurodegenerative diseases, and diabetes mellitus. Oxidative stress is linked to the development of many disorders.[4] Polyphenols are crucial in regulating the excessive formation of reactive oxygen species (ROS) and decreasing oxidative stress by adjusting the redox signaling pathways. Polyphenols have both antioxidant and pro-oxidant effects, with the latter being linked to their ability to induce apoptosis in cancer cells. Depending on their dosage and the specific cellular environment, polyphenolic substances can function as antioxidants or pro-oxidants.[5]

Polyphenols are crucial as they counteract free radicals, which can lead to cellular harm and play a pivotal role in chronic diseases such as cardiovascular illnesses, cancer, and neurological disorders. They possess anti-inflammatory characteristics that aid in the prevention and management of inflammatory disorders. Polyphenols are associated with cardiovascular benefits, including decreased blood pressure, enhanced blood vessel function, and reduced risk of heart disease.[6] They can also enhance cognitive function and lower the likelihood of neurodegenerative illnesses. Polyphenols support gut health by functioning as prebiotics, stimulating the proliferation of healthy gut flora. Polyphenols are bioactive substances present in plant-based foods that provide many health benefits such as antioxidant, cardiovascular, neuroprotective, and gastrointestinal health-promoting effects. Various classes within this category are categorized according to their structures, with polyphenols encompassing phenolic acids, stilbenes, flavonoids, lignans, and curcuminoids.[7]

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Quercetin

Quercetin (3,30,40,5,7-pentahydroxyflavone), the predominant flavonoid present in plants, fruits, and vegetables, originates from the Latin term "quercetum," which translates to oak forest. It is sometimes referred to as 3,30,40,5,7-pentahydroxy-2-phenylchromen-4-one.[8] Quercetin exists in two forms: as an aglycone or a glycoside. The presence of a functional glycosyl group connected to the skeleton impacts its solubility, absorption, and actions within a living organism. Quercetin glycoside in its conjugated form is absorbed more efficiently.[9] Quercetin offers several health advantages because of its antioxidant and anti-inflammatory characteristics. It functions as an antioxidant by eliminating free radicals and preventing oxidative stress, safeguarding cells from harm caused by ROS. Quercetin regulates inflammatory pathways, decreasing the likelihood of chronic conditions such as arthritis and cardiovascular disorders. It enhances cardiovascular health by enhancing blood vessel activity, reducing blood pressure, and maybe decreasing LDL cholesterol levels.[10] It boosts the immune system by increasing the effectiveness of immune cells and encouraging a well-regulated immunological reaction. Quercetin might possess neuroprotective qualities by diminishing oxidative stress and inflammation in the brain, which could help prevent neurodegenerative conditions such as Alzheimer's disease.[11]

Curcumin

Curcumin[1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione; diferuloyl methane] a component found in turmeric and utilized in traditional herbal medicine, is produced through a process involving DCS synthesizing feruloyldiketide-CoA and a curcuminoid scaffold (CURS) converting esters into curcuminoid structures.[12] While CURS has limited synthesis activity, combining it with DCS enhances efficiency. Curcumin performs keto-enol tautomerism, with the keto form being predominant in neutral and acidic conditions, and the enol form being stable in alkaline environments. Low bioavailability and hydrophobic properties result in inadequate absorption through the gastrointestinal tract. Contemporary encapsulation methods shield curcumin from deterioration, enhance water dispersal, and enhance bioavailability.[13] It offers several health advantages because of its anti-inflammatory and antioxidant characteristics. It blocks NF-kappaB, a protein that triggers genes associated with inflammation, hence decreasing inflammation on a molecular level. Curcumin is a powerful antioxidant that eliminates free radicals, protecting cells from oxidative harm. It can reduce symptoms and enhance joint function in illnesses such as osteoarthritis and rheumatoid arthritis. It can potentially penetrate the blood-brain barrier and be used to prevent or cure neurodegenerative conditions like Alzheimer's disease. Curcumin enhances cardiovascular health by enhancing endothelial function, decreasing inflammation, and serving as an antioxidant. It can aid in preventing and treating cancer by disrupting the formation, expansion, and dissemination of cancer cells and blocking angiogenesis.[14]

Anti-Cancer

Quercetin and curcumin, polyphenolic chemicals, are essential in cancer development as they regulate different cellular pathways such as proliferation, differentiation as well as apoptosis, and reactions to oxidative stress. Their anti-cancer properties are associated with their alteration of signaling pathways such as mTOR, PI3K, MAPK and Akt, as well as their impact on and oncoproteins such as RAS as well as tumor-suppressing protein particularly p53.[15] Polyphenols impact the expression and changes of the p53 gene, influencing its roles in DNA damage response, apoptosis regulation, cell cycle control, and senescence. Recent investigations have found that several chemicals have anti-cancer properties, with some demonstrating strong inhibition of proliferation in breast cancer cells. Curcumin blocked the PI3K/ mTOR/Akt signaling processes, reduced BCL-2 expression, and enhanced expression of Bax and cleavage of protein caspase-3.[16]

Quercetin and curcumin are natural chemicals characterized for their antioxidant and anti-inflammatory qualities, and have been researched for their potential in reducing toxicity. Quercetin functions as an antioxidant by neutralizing free radicals and decreasing oxidative stress, particularly acting as cytoxicity agents against cancer.[17] Quercetin has demonstrated anticancer qualities in laboratory experiments, however its function as a cytotoxic agent for cancer is intricate and reliant on the setting. Quercetin can trigger cell death, hinder the growth of cancer cells, and exhibit anti-angiogenic properties by reducing the development of new blood vessels that aid in tumor progression and spread. The antioxidant and anti-inflammatory effects of this substance may help in its possible anticancer capabilities by decreasing oxidative stress and inflammation. The effects of quercetin can be considerably influenced by its concentration, the specific form of cancer, and experimental settings. Quercetin's bioavailability can be limited, which makes achieving therapeutic levels by food difficult.[18]

Curcumin has also been studied for its potential anti-cancer properties. However, its role as a cytotoxic agent for cancer is complex and context-dependent. Curcumin's mechanisms of action include anti-inflammatory properties, antioxidant activity, apoptosis induction, and inhibition of cell proliferation. Its bioavailability is low, and achieving therapeutic concentrations can be challenging. The effectiveness of curcumin may vary depending on the type of cancer, molecular characteristics of cancer cells, and other factors. Clinical trials evaluating curcumin's efficacy in cancer treatment are being conducted continuously. Some studies suggest potential benefits, while others show limited impact. It is crucial to approach these findings with caution and consult with healthcare professionals for guidance on incorporating curcumin or other supplements into their cancer management plan. Curcumin should not be considered a standalone treatment for cancer and should be discussed with a healthcare provider as part of an overall treatment strategy.[16]

It possesses anti-inflammatory properties by regulating inflammatory pathways, which aids in reducing inflammation caused by exposure to toxins. Curcumin aids the body's detoxification mechanisms by boosting the function of detoxifying enzymes and eliminating free radicals. Research indicates that the mixture of these substances may have synergistic impacts, offering improved antioxidant and anti-inflammatory assistance. Both chemicals exhibit protective properties on organs, such as the liver and kidneys, which are crucial for detoxification processes. Individual responses may vary; thus, it is important to utilize these chemicals cautiously and consult a healthcare practitioner.[18]

METHODS

In our meta-analysis study, in which we did not specify any time period, we discussed studies from past to present indicating that Quercetin and Curcumin have protective effects in cancer research. The oldest research dated back to 1972, and studies from that day until 2023 were discussed. Detailed information is given on Figure. PRISMA Diagram and Table 1. MeSH employed in search strategy.

Table 1. MeSH employed in search strategy

"Quercetin" AND/OR "Curcumin" AND/ OR " Management"	"Curcumin" AND/ OR "protective effects" AND/ OR "oncogenesis"
"Quercetin" AND/OR "antioxidant" AND/ OR "treatment "	"Quercetin" AND/OR "Dietary Compounds" AND/ OR "Oxidative Stress"
"Quercetin" AND/OR "Tumor suppression" AND/ OR "therapeutics of curcumin"	"Quercetin" AND/ OR "Antiproliferative" AND/ OR "Molecular Pathway"

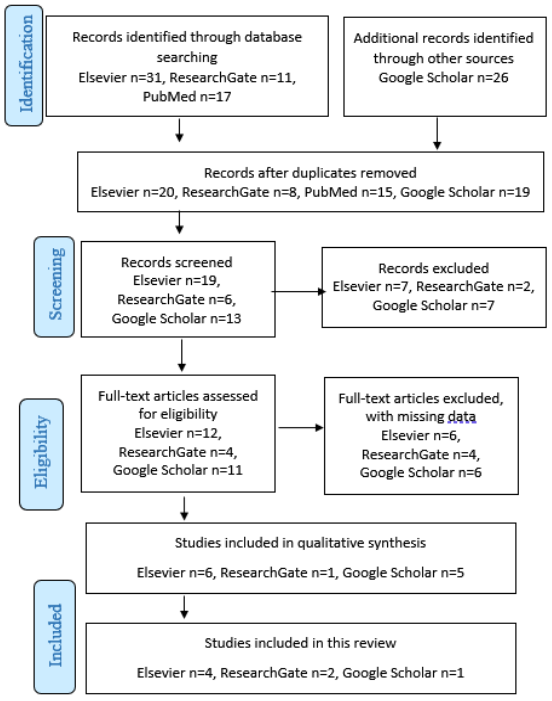

Figure. PRISMA diagram

Ethics committee permission is not required for this study. The researchers declare that they prepared this study in full compliance with all scientific publication ethical principles.

Inclusion & Exclusion Criteria

The review's inclusion and exclusion criteria are set to identify the chosen and qualified studies for the study investigation to align with the subject of interest. This study examines the protective effects of curcumin and quercetin against cancer, specifically investigating the relationship between cancer and dietary components. The investigations were conducted in English and underwent peer review, demonstrating scientific rigor and accuracy through intellectual contributions across all research components. The exclusion criteria focused on excluding studies that had incomplete or missing literature. Research conducted in languages lacking translations is excluded to maintain linguistic coherence and inclusivity. The standards improve precision and accuracy, which are essential for sustaining the methodological integrity of study evaluations.

Study Selection

In this study, research articles reporting the protective effects and anti-cancer properties of curcumin and quercetin in cancer studies were reviewed. The research is conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses to ensure its effectiveness. This study was performed according to PRISMA guidelines.[19] Search tools use the "And" operator in Boolean logic to include all variables in the search and confirm their presence in several databases. Various medical subject headings (MeSH) were used to search for information in the article. The study was conducted using many scientific databases such as Elsevier, National Library of Frontiers, ResearchGate, Scopus Medicine (Pubmed), Central (PMC), and Google Scholar. This article was searched using various medical subject headings (MeSH) such as "Quercetin," "Curcumin," "anticancer," "chemoprevention," "apoptosis," "Tumour suppression," "oncocancer," "anti-proliferative," and "oxidative stress" to conduct the research. Table 1 includes the MeSH terms used to search different databases.

Data Extraction

During the process of assisting with the methodical analysis and selecting the publications, the data management system made a substantial contribution. This contribution was significant. A methodical technique was applied in the research in order to locate and evaluate relevant articles in a rigorous manner. This was done in order to guarantee the accuracy and dependability of the findings. Throughout the entire process, the PRISMA standards were adhered to. This included conducting an in-depth analysis of the abstract and title of the paper, as well as conducting a comprehensive review of papers that were suitable for consideration, and so on. A PRISMA figure that was utilized in the process of identifying the research may be found in Figure. The meticulousness with which the appropriate clinical trial was selected and organized was the factor that ensured the dependability and precision of the findings.

RESULTS

A total of 85 records were identified through database research, from past to present. These consisted of Elsevier=31, ResearchGate=11, PubMed=17 and additional Google Scholar=26 studies, respectively. The oldest research dated back to 1972, and studies from that day until 2023 were discussed. Thirty-eight studies consisting of controlled cell culture studies were included in the final analysis. Detailed information is given on Figure PRISMA Diagram.

The meta-analysis results are shown in Table 2. Articles analyzing the protective effects of Curcumin and Quercetin; 3 of them are studies on breast cancer, 2 on colon and rectal cancer, 1 on lung cancer and 1 on bone cancer.

Quercetin's Maximum IC50 Concentration is 290μM while minimum is 5.14μM. Maximum IC50 Concentration of Curcumin is >80μM while minimum is 1.32μM.

The protective effects of both bioactive components appear to be reported in almost all Cell stages. All other details are shown in Table 2.

DISCUSSION

Quercetin and curcumin are polyphenolic compounds that may play important roles in regulating cancer development by managing various cellular processes like differentiation, apoptosis, the cell cycle, and responses to oxidative stress, in addition to antioxidants.[17] According to literature, Polyphenols control the expression of the p53 gene and its post-translational modifications like methylation, phosphorylation, acetylation, and ubiquitination. These modifications impact p53's roles in damage to DNA response, apoptosis regulation, cell cycle control, and senescence. Recent research has demonstrated the anti-cancer benefits of quercetin and curcumin, which can be linked to the various cellular pathways.[16] Also, Quercetin can reduce cyclin D1 and p38 MAPK phosphorylation by inhibiting Twist in MCF-7 breast cancer cells and cause G1/S arrest, leading to cell death. On the other hand, Curcumin can strongly suppress the growth of cancer cells such as MDA-MB-415, T47D and MCF-7. Curcumin can inhibit the cell cycle in M and G2 phase by reducing CDC25 levels as well as CDC25 levels and increasing p21 levels, which is a very important method to inhibit proliferation.[20]

Table 2. Characteristics of studies

Study	Cancer	Compound	Subject	IC50 Concentration	Cell stage	Bioactive Effect	Result
Ranganathan et al., 2015[20]	Breast	Quercetin	MCF-7 cancer cells	37μM	G1 arrest	Triggers cell death by inhibiting cyclin D1, p21, Twist, and phosphorylated p38MAPK.	Quercetin triggers cell death in cancerous breast cells by inhibiting Twist through the p38MAPK pathway.
			MDA-MB-231	100μM		No effect	
Hu et al., 2018[21]	Breast	Curcumin	MCF-7	1.32μM	Impairment in G2/M phase	Triggers cell death via reducing CDC25 and CDC2 levels, increasing P21 expression, inhibiting Akt/mTOR phosphorylation, decreasing BCL2, and enhancing Bax and cleavage caspase-3.	Curcumin fights breast cancer by inducing an arrest in the cell cycle at the G2/M phase, blocking Akt/mTOR signalling, and promoting caspase 3 protein cleavage, resulting in cell death.
			MDA-MB-231	11.32μM			
			MDA-MB-468	18.61μM			
			MDA-MB-415	4.69μM			
			T47D	2.07μM			
			SK-BR-3	16.39μM			
			BT-20	16.23μM			
Shen et al., 2020[40]	Breast	Curcumin	MCF-7	16.85μM	G1 phase was targeted	Decreases the levels of cyclin D1, cyclin E1, and CDK2. Triggers the mitochondrial apoptotic pathway.	B14 has more bioavailability as curcumin and combination with curcumin can hinder breast cancer by affecting mitochondrial apoptotic processes and cell cycle arrest.
			MDA-MB-231	42.01μM			
			MCF10A	>80μM			
Yang et al., 2016[24]	Colon	Quercetin	HT-29	81.65μM	G0 and G1 phase were affected	Decreases phosphorylated Akt, enhances CSN6 protein breakdown, leading to decreased levels of Myc and BCL-2, and increased levels of p53 and Bax.	Quercetin decreased the levels of phosphorylated-Akt and enhanced the degradation of CSN6 in HT-29 cells, leading to changes in the expression of Myc, p53, Bcl-2, and X proteins.
Shakibaei et al., 2013[25]	Colon rectal	Curcumin	HCT116	20μM	Antiproliferative effect in S phase	Enables mitochondrial disintegration and release of cytochrome c.	Curcumin and 5-FU may improve the therapy of chemoresistant colorectal cancer cells by targeting the NF-kB/PI-3K/Src networks and NF-kB-regulated products of genes.
			HCT116+ch3	5μM			
Zhaorigetu et al., 2021[28]	Lung	Quercetin	A549	5.14μM	G2/M cell cycle phases were affected	Upregulates Bax, downregulates BCL-2	Quercetin triggers programmed cell death in lung cancer cells, decreases MDA levels, boosts SOD and GSHP levels, and aids in the treatment of lung damage.
			H69	9.18 μM			
Suh et al., 2010[41]	Bone	Quercetin	HOS	290 μM	G1/S phase was arrested	Decrease in the expression of cyclin D1, a crucial cyclin for progression from the G1 phase to the S phase.	Quercetin induced programmed cellular death within human osteosarcoma (HOS) cells via transiently halting cells at the G1/S phase and triggering the capspase-3 pathway.

It has been reported that curcumin inhibits proliferation and triggers apoptosis in breast cancer series. Curcumin can inhibit phosphorylation along with activation of the Akt/mTOR cellular signaling pathway. It reduces the anti-apoptotic function of BCL-2 and increases Bax expression along with the cleavage of caspase-3 protein. Additionally, Analog B14 can inhibit the cell cycle in the G1 phase and trigger the mitochondrial death process by inhibiting the expression of cyclin D1 as well as the expression of cyclin E1 and also cyclin-dependent kinase 2.[21]

Another article reports that Quercetin treatment can reduce Cyclin D1 expression in ovarian SKOV-3 cells. The decrease in cyclin D1 expression may be related to the S and G1 phase of quercetin-treated cells.[22] Similarly, Curcumin application in SKOV3 cells reduced phospho-Akt as well as PI3K concentration levels, leading to an increase in caspase-3 and an increase in Bax levels. It also suppressed its anti-apoptotic effects by reducing BCL-2 levels.[23]

Quercetin treatment in human HT-29 colorectal cancer cells caused chromatin condensation, cellular shrinkage, as well as nuclear collapse. Quercetin reduces cell viability and may trigger cell death by inhibiting the signaling axis of Akt-CSN6-Myc. It is stated that quercetin also reduces the levels of p-Akt-Thr308 by reducing CSN6 protein expression levels. This resulted in decreased Myc concentration and increased p53 levels.[24]

In another study that we discussed within the scope of meta-analysis, it is reported that Curcumin increases the effectiveness of chemotherapy in colorectal cancer. An intervention combining 5-fluorouracil and curcumin on HCT116+ch3 cancer cell resulted in the activation or degradation of PARP as well as pro-apoptotic proteins such as Bax and caspase-8. Moreover, it reduced the levels of the anti-apoptotic protein BCL-XL and the proliferative protein of cyclin D1. 5-fluorouracil increased NF-κB/Src protein kinase cellular signaling pathway, while curcumin down-regulated by inhibiting IκBα phosphorylation.[25] Also, The H446 human small cell lung cancer (SCLC) cell line had the highest sensitivity to curcumin when analyzed against HCT116, Hela or PC-9 and A549 cells. H446 effectively induced cell death, decreased BCL-2 expression, and increased Bax expression, which has a potential role in controlling cell growth. Quercetin inhibited the growth of human lung cancer cells by activating Bax and caspase-3.[26]

Quercetin is noted to inhibit the growth of T24 cells as well as human bladder cancer 5637. Treatment with quercetin may trigger apoptosis by increasing caspase-3/7 activity, leading to a high rate of DNA fragmentation in the sub-G0/G1 phase. Quercetin has dual functions in inducing apoptosis and promoting protective autophagy. This treatment led to a gradual increase in LC3-II, an autophagic marker protein, in 5637 and T24 cells, along with the production of autophagosomes. Quercetin promoted a transition from autophagy suppression by Baf1 and chloroquine to apoptosis. The data showed that the reduction in cell viability and the rise in LC3-II processing were lessened in cells treated with quercetin that had been pre-treated with N-acetyl cysteine, a scavenger of ROS. This indicates that the cytotoxic effects and autophagy triggered by quercetin were caused by the production of ROS.[27,28] On the other hand, Quercetin-losartan (a drug used to treat hypertension) hybrid can alter the cell cycle, leading to cell cycle arrest, leading to cytotoxic activities, and reducing the proliferation and angiogenesis of cancer cells in glioblastoma cultures. It is stated that quercetin can inhibit angiogenesis by reducing segment and network formation of vessels.[29] Similarly, in human glioma cells, Curcumin has shown promising anti-cancer effects by increasing ROS generation. While it reduces cell viability, it may lead to increased autophagy and cell death. Curcumin and its analogs, including demethoxy curcumin, bisdemethoxy curcumin, and dimethoxy curcumin, are noted to induce premature cell death and ROS generation via apoptosis in LN229 and GBM8401 glioma cells in vitro. Quercetin and curcumin dosage has been shown to be an important factor in inducing cell death in three different leukemic cell lines (Nalm6, K562 and CEM). While it showed low sensitivity with an IC value of 160 micromolar in breast cancer T47D cells, it led to cell cycle arrest in S phase during tumor regression.[30,31]

The articles we have discussed show that Quercetin and curcumin are compounds that can prevent the growth of cancer cells by stimulating apoptotic pathways. Quercetin can lead to DNA damage leading to increased p53 expression, decreased antiapoptotic protein BCL2, and cleavage of the apoptosis signal MCL1. The decrease in mitochondrial membrane potential causes the release of cytochrome c and SMAC/DIABLO, which in turn activates the mitochondrial intrinsic pathway. Thus, mitochondria can work more efficiently. Inhibitors of apoptosis proteins (IAPs) can be inhibited by SMAC/DIABLO, and the release of cytochrome c from mitochondria leads to the activation of caspases.[32] Also, cytochrome c plays a role in the activation of caspase-9, which in turn cleaves caspase-3 and activates it.[33] Similarly, Curcumin can lead to cell cycle arrest and apoptosis by affecting the levels of cell cycle and cell death-related proteins in acute myeloid leukemia cell lines ML-2 and OCI-AML5.[34]

Research shows that Quercetin and curcumin's anti-cancer properties affect cancer development by altering various cellular signaling pathways as well as affecting non-cancer signals such as PI3K/Akt, Wnt/β-catenin, JAK/STAT, MAPK, p53, NF-kB, and by affecting non-coding RNAs (ncRNAs).[35] Non-coding RNAs have a crucial role in various physiological processes such as chromatin restructuring, transcription, post-transcriptional modifications and signal transduction. Dysregulated non-coding RNAs may contribute to cancer development by acting as oncogenes or tumor suppressors, highlighting their potential for cancer therapy. ncRNAs, especially microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), are highly important targets in the anti-cancer properties of polyphenols. They target key oncogenes or restore tumor suppressor gene expression. In contrast to well-studied miRNAs, lncRNAs have only recently been recognized as important factors in fighting cancer.[36] It has been reported that quercetin and curcumin can modulate miRNA function by decreasing oncogenic miRNA or increasing tumor

suppressor miRNA. This effect can affect multiple genes and affect signaling pathways that regulate cell growth and death.[36] Quercetin's ability to suppress the growth of MCF-7 cells is likely due to its ability to decrease miR-21 expression and raise the production of PTEN, which are the targets of miR-21 and are crucial in the apoptotic pathway.[37] In addition, a mixture of quercetin and hyperoside inhibits the expression of miR-21 linked with prostate tumors, leading to decreased invasion, and spread of cancer PC3 cells of prostate. This combination may lead to an increase in the production of cell death protein 4 (PDCD4), an important target protein of miR-21, which is repressed by miR-21. Overexpression of miRNA344a-3p mimic along with curcumin treatment may result in increased levels of apoptotic proteins such as procaspase-9 and cleaved caspase-3 in RT4 schwannoma cells. On the other hand, Curcumin inhibits osteogenesis by upregulating miR126a-3p, which directly targets and inhibits human low-density lipoprotein receptor-related protein 6 (LRP6) expression. This effect inhibits osteogenic differentiation by suppressing the WNT signaling pathway. Therefore, long-term or high-dose use of curcumin may inhibit bone formation, resulting in decreased bone mass and density, thereby causing tumor spread.[38,39]

CONCLUSION

The antioxidant, cardiovascular, neurological, and gastrointestinal health-promoting actions of polyphenols, such as quercetin and curcumin, are only some of the many health benefits that polyphenols provide. Through the influence that they exert on a variety of cellular processes and signaling pathways, these substances have been demonstrated to possess anti-cancer capabilities. Through processes such as triggering apoptosis, blocking cellular signaling pathways, and altering non-coding RNAs, studies have revealed that quercetin and curcumin have the potential to be used in the prevention and treatment of cancer. The protective effects of both bioactive components, especially through their strong antioxidant properties, are perhaps among the most researched functional food studies in the literature. However, elucidating the synergistic mechanisms through which the protective effects of both components on cancer and the positive/negative effects they will exert through detailed research can make a significant contribution to the literature. In addition, it is thought that it would be useful to examine these functional components with nanoparticle applications, which have become increasingly popular in recent years, and to evaluate them in detail with clinical studies that are less available in the literature, such as tumor development, angiogenesis and metastasis. Before adding quercetin and curcumin, which appear to be effective against breast, colon, and lung cancers, to cancer management strategies, detailed analyzes are required and it is important to seek advice from experts in this field.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethics committee approval is not required for this study.

Informed Consent

Informed consent form is not required for this study.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors have contributed equally to this work and share first authorship.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1469413
J Health Sci Med. 2024;7(3):321-326

Acute rheumatic fever: a single center experience

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Cite this article as: Tunçer T. Acute rheumatic fever: a single center experience. *J Health Sci Med.* 2024;7(3):321-326.

Received: 17.04.2024 ◆ **Accepted**: 12.05.2024 ◆ **Published**: 27.05.2024

ABSTRACT

Aims: Acute rheumatic fever continues to be a serious public health issue globally and in our country. The aim was to evaluate the socioeconomic, clinical characteristics, and echocardiographic findings of patients diagnosed with acute rheumatic fever in the Sancaktepe district of Istanbul province, and to compare them with Turkiye and global data.

Methods: The study was conducted retrospectively by reviewing the hospital records of 22 patients who presented to the pediatric cardiology outpatient clinic of Sancaktepe Training and Research Hospital and were diagnosed with acute rheumatic fever between March 2018 and October 2021. Demographic and socio-economic data, complaints, physical examination findings, clinical and laboratory features, initial echocardiographic findings at presentation, and follow-up data of the patients were identified.

Results: Out of the 22 patients diagnosed with acute rheumatic fever, 13 (59.1%) were male, with a mean age of 131.9 months ±32.9. The patients were followed up for an average of 23.2±11.5 months. Most patients (36.3%) presented during the winter months. The average number of individuals living in the patients' households was found to be 5.8±1. It was observed that 95% of the mothers and 45.5% of the fathers had completed primary education, none of the mothers were employed, and all employed fathers received minimum wage. A family history of acute rheumatic fever was present in 18.8% of the patients. When echocardiographic findings were evaluated, valve involvement was detected in 90.9% of the patients. While single valve involvement was observed in the majority (72.7%) of patients, mitral valve involvement was most common (81.8%). During the follow-up period, complete resolution was observed in 45.5% of patients with mild mitral regurgitation and 66.6% of patients with mild aortic valve regurgitation.

Conclusion: While the majority of the data in the study are consistent with the literature, attention has been drawn to the challenges associated with the low socioeconomic status of our patient population. With the increase in socioeconomic status in our country, as in developed countries around the world, the incidence of disease may decrease.

Keywords: Acute rheumatic fever, social class, echocardiography

INTRODUCTION

Acute rheumatic fever (ARF) emerges as an immunologically mediated and non-suppurative complication of group A streptococcal infection. It affects the heart, joints, central nervous system, skin, and subcutaneous tissue. While the incidence of ARF has decreased in Europe and North America due to preventive measures, it continues to be a significant public health issue in developing countries.[1,2] The diagnostic criteria for ARF were established by Jones in 1944 and were last updated by the American Heart Association (AHA) in 2015.[3] According to the Jones criteria revised by the AHA in 2015; populations are divided into two risk groups, low-risk and moderate-to-high-risk. In the presence of reliable epidemiological data, an ARF incidence of ≤2/100,000 school-aged children (usually aged 5-14 years) per year or a prevalence of rheumatic heart disease of ≤1 per 1000 population of all ages can be considered low-risk. While the global incidence of ARF varies by geographical region and population, the average global incidence of ARF is 19/100,000.[2] In developed countries, this incidence ranges from 0.5 to 3/100,000, while in developing countries; it varies between 20 and 200/100,000.[1,4,5] Various studies on the incidence of ARF have been conducted in different geographical regions and cities in Turkiye at different times, but the multicenter national study conducted in 2016 is the most recent and comprehensive.[6-11] In this study, the incidence of ARF for Turkiye was determined to be 8.84/100,000.[11] When evaluated in terms of geographical regions, the highest incidence was found in the Eastern Anatolia region (14.4/100,000), while the lowest incidence was observed in the Black Sea region (3.3/100,000).

The clinical profile of ARF generally shows similarities between low-risk and moderate-to-high-risk groups, with the most common findings worldwide being arthritis (35%-66%) and carditis (50%-70%). These are followed in frequency by chorea (10%-30%), subcutaneous nodules (0%-10%), and erythema marginatum (<6%).[3] In the largest series study conducted in our country, based on data collected from all geographical regions, clinical carditis (53.5%) was the most frequently detected finding among 1103 patients diagnosed with ARF between January 1 and December 31, 2016.[11] This

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was followed by polyarthritis (52.8%), subclinical carditis (29.1%), polyarthralgia (18.6%), aseptic monoarthritis (10.3%), Sydenham chorea (7.9%), and erythema marginatum (0.4%), while subcutaneous nodules were not observed.

According to the data from the Turkish Statistical Institute's 2021 census, the total population of Sancaktepe district in Istanbul province is 474,668, which is greater than the population of 47 provinces in Turkiye.[12] In 2022, The Ministry of Industry and Technology of the Republic of Turkiye conducted a research to determine the socio-economic development ranking of districts in Turkiye. Sancaktepe district is ranked 95th and is 34th among the 39 districts of Istanbul.[13] This study was conducted to reveal the demographic characteristics, socioeconomic status, clinical characteristics, and follow-up results of patients diagnosed with ARF at the Pediatric Cardiology Clinic of Sancaktepe Training and Research Hospital in Istanbul province's Sancaktepe district. The aim of the study is also to compare these findings with data from around the world and Turkiye.

METHODS

The study was carried out with the permission of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Scientific Researches Ethics Committee (Date: 24.03.2021, Decision No: 2021/124). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. As it is a retrospective study, consent was not obtained from the parents of the patients. Missing data regarding socioeconomic status in the files were completed by reaching out to individuals via telephone.

The study was conducted by retrospectively reviewing patients who presented to the Pediatric Cardiology Clinic of Sancaktepe Training and Research Hospital in Sancaktepe district of Istanbul province between March 2018 and October 2021. Patients were identified from the hospital's medical record system. Patients who were diagnosed with ARF for the first time in the clinic between the specified dates were included. The diagnosis of ARF was made according to the updated Jones criteria in 2015.[3] Patients with either two major criteria or one major and two minor criteria in the presence of a history of preceding infection were considered to have active ARF. In distinguishing between physiological and pathological valve insufficiency, the Doppler revision criteria for rheumatic valvulitis were used.[3] According to these criteria, the following conditions must be met for both the mitral and aortic valves: insufficiency observed in at least two imaging planes, peak velocity >3 m/s, pansystolic jet for the mitral valve, pandiastolic jet for the aortic valve, insufficiency jet length ≥2 cm for the mitral valve (in at least one imaging plane), and insufficiency jet length ≥1 cm for the aortic valve (in at least one imaging plane). Demographic information, presenting complaints, and examination findings of the patients were recorded. Laboratory tests including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum antistreptolysin-O (ASO) levels were determined. Electrocardiographic and transthoracic echocardiographic findings were documented. Treatments and responses to treatment were recorded.

Aspirin (100 mg/kg/day) was administered to patients with arthritis and mild carditis for 2-4 weeks and then gradually tapered off. Prednisolone (2 mg/kg/day) was given to patients with moderate to severe carditis for 4-6 weeks, and aspirin was added to the treatment during the tapering period. As primary prophylactic treatment, a single dose of intramuscular benzathine penicillin was administered, while in secondary prophylactic treatment, benzathine penicillin G (>27 kg: 1,200,000 units, <27 kg: 600,000 units) was given every 21 days.

Socioeconomic status (SES) is a widely used concept in health research. Although researchers may have an intuitive understanding of what SES entails, numerous measurement methods demonstrate the complexity of the construct. There is no single best SES indicator that can be universally applied to all research purposes, settings, and time points. Each indicator measures different, often interrelated aspects of socioeconomic stratification and may be more or less relevant to different health outcomes and stages of life.[14] Therefore, in this study, questions were selected with a focus on life stages (such as the pediatric age group), and SES question types were chosen accordingly.[15]

Transthoracic echocardiography was performed using the Philips Affiniti 50 c echocardiography system (Philips Healthcare, Andover, MA, USA). The Philips S4-2 Cardiac Sector Probe and Philips S8-3 Cardiac Sector Probe were utilized. All cases were evaluated by the same pediatric cardiologist. Standard echo modes including M-mode, 2D, color, pulse and continuous Doppler, and tissue Doppler were employed.

Statistical Analysis

Statistical analysis was conducted using JASP (Jeffreys's Amazing Statistics Program, version 0.14.1.0, Department of Psychological Methods, University of Amsterdam, The Netherlands). Descriptive statistics were employed to summarize the demographic and clinical characteristics of the patients. Continuous variables were presented as mean±standard deviation (SD), while categorical data were expressed as numbers and percentages.

RESULTS

Between March 2018 and October 2021, a total of 22 patients were identified with a diagnosis of ARF. Among them, 13 (59.1%) were male and nine (40.9%) were female (male/female ratio: 1.44). The mean age was determined to be 131.9 months ±32.9 (minimum: 66 months and maximum: 181 months) (Table 1).

The mean body weight and height of the patients were determined to be 39.2±12.4 kg and 144.18±13.7 cm, respectively, with percentile means of 49.4±19.7 and 47.1±21.3. For patients diagnosed only with clinical carditis and/or polyarthritis, the mean body weight and height percentile means were found to be 37.9±17.4 and 32.5±16.8, respectively. However, in all patients diagnosed with subclinical carditis and/or polyarthritis or polyarthralgia or only chorea, the mean body weight and height percentile means were determined to be 64±10.5 and 64.5±36.4, respectively.

Table 1. General characteristics of the study group and study results		
	Number	Percentage
Male	13	59.1
Female	9	40.9
Complaints at admission		
Joint pain	14	63.6
Fever	7	13.6
Audible murmur during examination	6	27.2
Chest pain	4	18.8
Elevated ASO levels	2	9
Physical examination findings		
Pansystolic murmur at mitral area	12	54.5
Arthritis	11	50
Chorea	1	4.5
Signs of heart failure	1	4.5
Major and minor findings		
Clinical carditis	12	54.5
Subclinical carditis	6	27.2
Polyarthralgia	4	18.1
Carditis+polyarthritis	9	40.9
Subclinical carditis+polyarthralgia	4	18.1
Fever	7	31.8
PR prolongation in ECG	3	13.6
Increased ESR	18	81.8
Increased CRP	17	77.2
Evidence of preceding group A streptococcal infection		
Elevated ASO levels	20	90.9
Positive throat culture	3	13.3

ASO: Serum antistreptolysin-O, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

The average number of individuals in the households where the patients lived was determined to be 5.8±1. When questioned about the mother's education level, it was found that one mother was illiterate, while the rest (95%) had completed primary school. Regarding the father's education level, it was found that ten (45.5%) had completed primary school, seven (31.8%) had completed middle school, and five (22.7%) had completed high school. When asked about employment status, all mothers stated that they were not working, while all fathers except one stated that they had a job available. It was noted that all working fathers earned minimum wage. When asked about homeownership, 12 families (54%) stated that they owned their homes. Regarding the type of housing, six families (27.2%) lived in slums, six families (27.2%) lived in detached houses, and ten families (45.4%) lived in apartment buildings. None of the patients had their own rooms. All parents of the patients reported that they had migrated from Eastern and Southeastern provinces to Sancaktepe within the last 20 years.

The patients were followed for an average of 23.2±11.5 months (minimum 3 and maximum 42 months). When the timing of patient admissions was examined, it was found that they most commonly occurred during the winter months (Table 1). A history of acute rheumatic fever was present in four patients' families (18.8%).

The patients' presenting complaints, physical examination findings, and major and minor criteria identified in the patients are shown in Table 1. None of the patients had erythema marginatum, subcutaneous nodules, or monoarthritis detected. One patient (4.5%) was classified as having severe carditis, two patients (9%) had moderate carditis, and 17 patients (77.2%) had mild carditis. One patient was recorded as having arthritis, and one patient was noted to have chorea.

When laboratory findings were examined, the mean C-reactive protein and erythrocyte sedimentation rate were found to be 13.2±7.7 mg/dL and 47.4±18.1 mm/hour, respectively. Throat cultures were taken from all patients, and ASO titers were tested (Table 1).

When transthoracic echocardiography findings were evaluated, valve involvement was observed in 20 patients (90.9%). While most patients had involvement of a single valve, mitral valve involvement was most common (Table 2). The mean length of mild mitral regurgitation jet was measured as 2.2±0.11 cm, and the mean length of moderate mitral regurgitation jet was measured as 3.3±0.17 cm. Severe mitral regurgitation was detected in only one patient (4.5%), who also had moderate aortic valve regurgitation.

Table 2. Transthoracic echocardiography findings		
	Number	Percentage
Valve involvement	20	90.9
Single valve involvement (mitral or aortic valve)	16	72.7
Dual valve involvement (mitral and aortic valve)	4	18.1
Mitral valve involvement only	14	63
Aortic valve involvement only	2	9
Mild mitral regurgitation	11	50
Moderate mitral regurgitation	6	27.2
Severe mitral regurgitation	1	4.5
Mild aortic regurgitation	2	9

Mild aortic valve regurgitation was detected in two patients (9%) who had only aortic valve involvement (Table 2). One patient had mild aortic valve regurgitation along with moderate mitral valve regurgitation, while two patients had severe aortic valve regurgitation along with moderate and severe mitral valve regurgitation, respectively. The mean length of the aortic regurgitation jet was recorded as 1.78±0.58 cm.

During the follow-up period, among the 11 patients with mild mitral regurgitation, complete resolution was observed in five patients (45.5%), while no change was observed in five patients (45.4%). In one patient, there was no improvement and aortic valve regurgitation was added to the condition. Among the six patients with moderate mitral regurgitation, two patients (33.3%) had their moderate regurgitation converted to mild regurgitation, while three patients (50%) persisted with moderate regurgitation, and one patient had aortic valve regurgitation added to the existing condition. Among the three patients with mild aortic valve regurgitation, improvement was observed in two patients (66.6%), while one patient persisted with the condition. Among the two patients with moderate aortic valve regurgitation, one patient's condition improved to mild, while no change was observed in the other.

DISCUSSION

Although acute rheumatic fever is preventable and treatable, it unfortunately remains a significant health issue worldwide. It is particularly prevalent in developing and underdeveloped countries and stands as one of the leading causes of acquired heart disease.[1,3,4]

In the most recent multicenter national study conducted in Turkiye in 2016, the incidence of acute rheumatic fever was determined to be 8.84/100,000.[11] In this study, the incidence in the Marmara region, which includes the Sancaktepe district, was found to be 6.6/100,000. Although this value is lower than the incidence nationwide, it is higher than the incidence figures in developed countries. The distribution of age, gender, and time of presentation of patients diagnosed with acute rheumatic fever in our study is similar to the current data in Turkiye.[11,16,17] However, in some studies conducted in Turkiye with a small number of patients, the gender distribution shifted towards females, and the disease was found to be more prevalent in the spring season.[18-20] When compared with other countries around the world, both our study and the current data in Turkiye show similarities in age distribution. However, in studies conducted in different geographical locations such as Fiji, Australia, New Zealand, and Thailand, unlike Turkiye, the disease was found to be more common in females, with peaks even occurring in August in New Zealand.[21-24]

It is noteworthy that the average weight and height percentiles of the patients in our study were found to be below the 50th percentile. While all patients with subclinical carditis and/or polyarthritis or polyarthralgia or only chorea had weight and height percentiles above the 50th percentile, those with only clinical carditis and/or polyarthritis were found to be below the 50th percentile. This situation may be associated with the population of the Sancaktepe district, especially consisting of citizens who have migrated from the Eastern and Southeastern Anatolia regions. Indeed, 305,016 (64.2%) of the district's population of 474,668 are from these regions and are socioeconomically disadvantaged.[12] Coffey et al.[25] investigated the relationships between factors affecting health such as living in crowded environments, education level, family income level, and social structure, and the prevention of and risks for Group A streptococcal infection, acute rheumatic fever, and rheumatic heart diseases in their systematic review study. They found a positive relationship between living in crowded environments, nutritional level, parents' education and employment status, and acute rheumatic fever. Similarly, Stacey et al.[24] in their study conducted in Australia where they published the long-term outcomes of patients with acute rheumatic fever, showed that more than half of the patients (52.1%) were of low socioeconomic status. The data I collected regarding the socioeconomic levels of the patients in our study also supports this finding.

When comparing the complaints of the patients in the study with the previous studies, it was observed that a large majority of previous studies focused more on physical examination findings rather than patient complaints. In our study, joint pain was the most common complaint, followed by fever. In previous studies, joint pain has been reported as the most common complaint.[16,26,27]

Considering the physical examination findings, in our study, arthritis was the most common, followed by carditis, which is consistent with the literature findings. Similar to my study, in most studies with a small number of patients, except for one, erythema marginatum and subcutaneous nodules were not encountered.[20] In the recent study covering data from all over Turkiye, subcutaneous nodules were not found, and erythema marginatum was determined to be 0.4%.[11]

Carditis, seen in 30-80% of patients, is the most important major manifestation that determines the prognosis of the disease.[3,28] When cardiac findings were examined in detail in our study, clinical carditis was observed in 54.5% and subclinical carditis in 27.2% of patients. My data are consistent with the recent multicenter study data from our country and global data.[3,4,11,28-30] However, in most of the similar single-center studies conducted in our country, patients were not examined with a distinction between clinical carditis and subclinical carditis.[16,18,20] In one of the studies where this distinction was made, the rates for clinical carditis and subclinical carditis were found to be 48% and 36%, respectively, while in another study, they were determined to be 30.7% and 36%.[19,31] The first of these studies was conducted in Erzurum, while the other was conducted in Ankara. The results of the study conducted in Erzurum are similar to my study, as both study populations originate from similar geographical regions and likely represent similar socioeconomic classes. Subclinical carditis can be observed in a wide range of 0% to 53% worldwide.[3] In a study conducted in Bangladesh in 2023, 64.9% of patients with detected carditis were classified as subclinical carditis.[32] This situation can be explained by the widespread use of echocardiography.[3] However, delays in accessing healthcare due to socioeconomic reasons, as possible in our study, may increase the likelihood of patients being diagnosed with clinical carditis to a greater extent.

When joint findings were evaluated, polyarthritis or polyarthralgia was detected in 68.1% of patients in our study, while no patients were found to have monoarthritis or monoarthralgia. The data are consistent with the literature data regarding polyarthritis or polyarthralgia, but the absence of monoarthritis or monoarthralgia may be explained by the small size of the study population.[3,4,11,16-20,28,31,32] There are studies with relatively few patients where monoarthritis or monoarthralgia was not detected (number of patients ranging from 34 to 55).[17-20] Moreover, even in the most recent and comprehensive study including 1103 patients, monoarthralgia was reported as 1.6%.[11]

When the minor criteria of ARF (CRP, ESR, Fever, PR prolongation in ECG, etc.) and evidence of preceding Group A streptococcal infection (ASO and throat culture) values were examined in our study, they showed similarities with single-center studies conducted in our country, as well as with recent multicenter studies and studies conducted in different countries around the world.[11,16,18-20,30,31,33-35] Unlike other studies, monoarthralgia was not observed among the minor criteria in our study. This could be attributed to the small sample size in our study, as mentioned earlier. Although throat cultures were obtained from all patients and ASO titers

were determined in our study, only three patients (13.3%) had positive findings for group A beta-hemolytic streptococci in throat cultures, while elevated ASO levels were detected in twenty patients (90.9%), which may be associated with the use of antibiotics before referral by the patients.

Considering the data obtained from transthoracic echocardiography, the detection of valvular involvement in 90.9% of the patients exceeds the current data in our country (82.6%) and is closer to the data from our Eastern Anatolia region (86.3%). Gasimova et al.,[18] in their study conducted at Selcuk University Faculty of Medicine Hospital between 2017 and 2019, found valvular involvement in 89% of the patients, which is the closest value to my study. In the majority of patients in our study, single-valve involvement (72.7%) was observed, predominantly affecting the mitral valve (81.8%). Simultaneous involvement of the aortic and mitral valves was detected in 18.1% of the patients. Evaluation of clinical and transthoracic echocardiography findings in patients with acute rheumatic fever in studies conducted in various countries around the world and in our country has consistently identified the mitral valve as the most commonly affected valve, as in our study.[9,16,17,20,29,30,32,34,36] Simultaneous involvement of the aortic and mitral valves has been found in studies conducted in our country with percentages of 17.6%, 24.4%, 33.9%, 44.4%, and 45.5%, which are mostly higher than our data.[16,17,20,31,33] Considering global data, Kaewpechsanguan et al.,[35] in their study with 81 children in Thailand, found dual-valve involvement in 72.8% of the patients, while Alam et al.,[32] in their study with 100 patients in Bangladesh, found this rate to be 12%, similar to my study. Although not detected in our study and most studies conducted in our country, tricuspid regurgitation due to ARF has been reported in a wide range of 2-44% in the literature.[16,22,30]

In our study, complete resolution of mild mitral regurgitation was observed in 45.5% of the patients, and complete resolution of mild aortic regurgitation was observed in 66.6% of the patients. Yılmaz et al.[16] found that in 65 patients with ARF followed for an average of 12 months, mitral regurgitation improved in 21.4% of the patients and aortic regurgitation improved in 40% of the patients, without specifying the degree of regurgitation. In another study conducted with 55 patients in our country, it was found that mitral regurgitation improved in 6.1% of the patients and aortic regurgitation improved in 36.6% of the patients.[18] The low rate of improvement in mitral valve regurgitation in this study does not seem consistent with both my study and the literature data. In another study conducted in our country, which included 160 patients over seven years, it was found that mild mitral regurgitation completely resolved in 45% of the patients, and aortic regurgitation completely resolved in 55.9% of the patients, consistent with my study.[31] Considering data from other countries, in a study evaluating 75 patients, it was found that after treatment, regurgitation decreased by 64% in all patients without specifying the valve.[21] Kaewpechsanguan et al.[35] found that after one year of follow-up, 43.4% of patients with moderate to severe mitral regurgitation and 41.7% of patients with moderate to severe aortic regurgitation regressed to clinically insignificant mild regurgitation. However, in the same study, it was also shown that 4.3% of initially clinically insignificant mild mitral regurgitation and 3.6% of initially clinically insignificant mild aortic regurgitation progressed to clinically significant regurgitation.

Limitations

The number of patients included in the study is one of the limiting factors. Although the population density of the district where the study was conducted is higher than many other cities in Turkiye, ultimately it is a district in Istanbul. Another shortcoming of the study is the relatively short follow-up period. There are studies in the literature covering 8 to 27 years.[29,30]

CONCLUSION

Acute rheumatic fever remains an important health problem in childhood in our country, and even in a district of Istanbul, which is one of the largest cities in our country. While the majority of the data in our study are consistent with the literature, attention has been drawn to the challenges associated with the low socioeconomic status of our patient population. It is believed that with the increase in socioeconomic status in our country, as in developed countries around the world, the incidence of the disease will decrease.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Scientific Researches Ethics Committee (Date:05.07.2023, Decision No: 2023-25).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The author has no conflicts of interest to declare.

Financial Disclosure

The author declared that this study has received no financial support.

Author Contributions

The author declares that he has all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1469719
J Health Sci Med. 2024;7(3):327-331

Comparison of mortality rates and risk factors for mortality between proximal femoral nailing and bipolar hemiarthroplasty for hip fractures

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Cite this article as: Altıntaş M, Ateş O. Comparison of mortality rates and risk factors for mortality between proximal femoral nailing and bipolar hemiarthroplasty for hip fractures. *J Health Sci Med.* 2024;7(3):327-331.

Received: 17.04.2024 ◆ **Accepted**: 12.05.2024 ◆ **Published**: 27.05.2024

ABSTRACT

Aims: The study aimed to compare in-hospital and post-discharge mortality rates and identify risk factors for patients who underwent bipolar hemiarthroplasty (BHA) or proximal femoral nailing (PFN) for hip fractures.

Methods: The files of 395 patients, consisting of 129 BHA and 266 PFN patients performed between January 2017 and October 2022, were analyzed retrospectively. The demographic characteristics of the patients, in-hospital and 1-year post-discharge mortality rates, and risk factors that may have affected these mortality rates were analyzed.

Results: There was no significant difference between the two groups in terms of demographic characteristics, intensive care unit (ICU) stay, American Society of Anesthesiologists (ASA) score, time to surgery, and intubation ($p>0.05$). The length of hospital stay and blood transfusion rates were higher in the BHA group ($p<0.05$). There was no significant difference between the two groups regarding in-hospital and 1-year post-discharge mortality rates ($p>0.05$). The 1-year post-discharge mortality rates were higher for patients with a higher mean age, longer length of hospital stay, longer length of ICU stay, time to surgery (>48 h), for patients who underwent intubation and blood transfusion, and for those with an ASA score of 4 ($p<0.05$). Chronic obstructive pulmonary disease (COPD) and congestive heart disease (CHF) were associated with higher in-hospital and 1-year post-discharge mortality, whereas dementia was only associated with higher 1-year post-discharge mortality ($p<0.05$).

Conclusion: There was no significant difference between the in-hospital and 1-year post-discharge mortality rates of patients who underwent PFN and those who underwent BHA. Patients with longer time to surgery (>48 h), longer length of hospital and ICU stay, patients with an ASA score of 4, and intubated patients had higher mortality rates. Comorbid CHF, COPD, and dementia increased the mortality rate in patients.

Keywords: Hip fracture, bipolar hemiarthroplasty, proximal femoral nail, mortality

INTRODUCTION

With technological advancements and higher socioeconomic statuses, life expectancy has increased significantly in the post-20th century period, especially in developed countries. A study conducted in Turkiye determined that life expectancy was 39.41 years in 1950, but the age increased to 77.77 years in 2020.[1] The increase in the elderly population and the corresponding increase in osteoporotic patients has led to a higher incidence of hip fractures caused by simple falls. The primary goal of hip fracture treatment is to mobilize the patient and help them return to daily life. Despite the high risk for mortality and morbidity, patients with hip fractures are operated on for this purpose. Outcomes in unoperated patients are poor.[2,3]

Proximal femoral nailing (PFN) and bipolar hemiarthroplasty (BHA) surgery have recently become the most commonly used options for hip fracture operations. The advantages of PFN include a smaller incision, a more biological approach with osteosynthesis, and less bleeding. In contrast, BHA requires no time for fracture union, has lower implant failure, and allows the patient to compress with full load postoperatively.[4,5]

Previous studies have reported that in-hospital mortality rates following hip fracture surgery vary between 2.7% and 15%, while 1-year mortality rates vary between 11.5% and 58.3%.[6] Many factors affecting mortality and morbidity in patients operated for hip fracture exist, including age, comorbidities, operation duration, and surgical technique.[7–9]

The main objective of this study was to compare in-hospital and post-discharge mortality rates for patients who underwent PFN for pertrochanteric fractures and BHA for femoral neck fractures. The secondary purpose was to determine the risk factors affecting mortality rates.

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METHODS

Institutional and researcher approval was obtained for the study. Ethical approval was obtained from the study was carried out with the permission of the University of Health Sciences Gazi Yaşargil Training and Research Hospital Clinical Researches Ethics Committee (Date: 13.01.2023, Decision No: 320); where all imaging and patient procedures were performed in a single center. There was no financial incentive to conduct the study, and all procedures were performed ethically and in accordance with the principles of the Declaration of Helsinki.

In the study, 395 patients who underwent PFN (Figure 1) (Zimed Medikal, Şehitkamil/Gaziantep/Turkiye) for pertrochanteric femur fractures and cementless BHA (Figure 2) (Zimed Medikal, Şehitkamil/Gaziantep/Turkiye) for femoral neck fractures between January 2017 and October 2022 were retrospectively analyzed. Exactly 129 patients underwent BHA, and 266 underwent PFN. Patients were first grouped according to whether they had gone through BHA or PFN surgery, and their in-hospital and 1-year post-discharge mortality rates, demographic characteristics, age, comorbid diseases, length of hospital stay, duration of surgery, length of intensive care unit (ICU) stay, and blood transfusion needs were compared. Patients who expired in the hospital were excluded. The differences between patients who died during the 1-year post-discharge period and those who survived in terms of demographic characteristics, surgeries performed, comorbid diseases, duration of ICU stay, intubation, blood transfusion, American Society of Anesthesiologists (ASA) physical status classification score,[10] time to surgery, and length of hospital stay were compared. Lastly, the effect of related parameters on mortality in patients who died in-hospital were analyzed. The 1-year post-discharge mortality of patients was verified using civil registry records. Precisely 162 of the patients were male, and 233 were female. Exactly 226 patients were operated on the right hip, and 169 patients were operated on the left hip. Patients with an ASA score of 2, patients who did not require a postoperative ICU stay, those exposed to high-energy trauma, patients <65 years of age, patients with pertrochanteric fractures who underwent calcar-supported BHA or cemented BHA, patients with pathologic fractures, those with multiple trauma, and patients who underwent revision surgery were excluded. The same group of experienced surgeons performed all operations. All patients were operated under spinal anesthesia. One gram of Cefazolin I.V. was administered to patients 30–60 min before surgery. Antithrombotic prophylaxis using low molecular weight heparin (Fraxiparine, GlaxoSmithKline, Brentford, UK) was administered in all cases. Patients undergoing PFN were performed on under traction on a traction table in the supine position, and patients undergoing BHA were performed on in the lateral decubitus position through a lateral incision. PFN patients were mobilized with partial load at the 24th postoperative hour, and BHA patients were mobilized with full load at the 24th postoperative hour under the supervision of a physiotherapist. Anterior-posterior and lateral radiographs were taken within 24 h post-operation to evaluate the position of the implant and the reduction of the fracture.

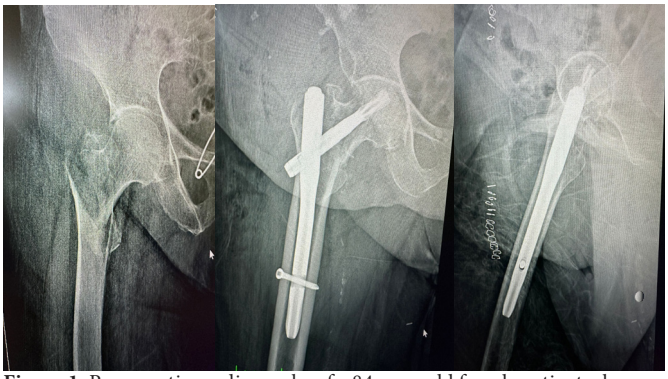

Figure 1. Preoperative radiographs of a 84-year-old female patient who underwent PFN due to pertrochanteric femur fractures (A); postoperative posterior-anterior (B1) and lateral radiographs (B2)

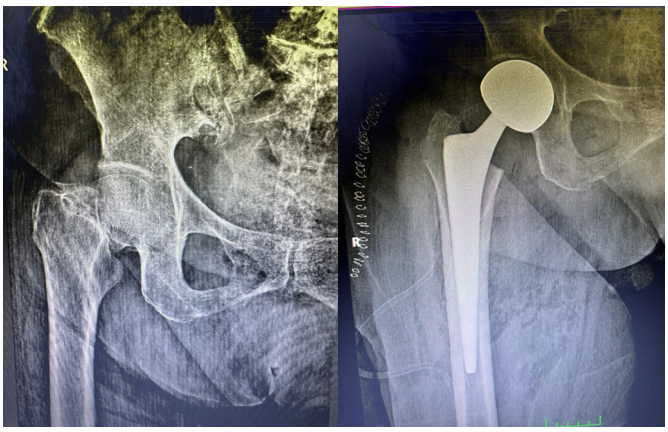

Figure 2. Preoperative radiographs of a 79-year-old female patient who underwent BHA due to femoral neck fractures (A); postoperative posterior-anterior radiographs (B)

Statistical Analysis

Statistical analyses were performed using the 2007 Number Cruncher Statistical System Statistical Software (Utah, USA) package program. Data were evaluated using descriptive statistical methods (mean, standard deviation, median, interquartile range). In addition, the Shapiro–Wilk normality test was used to determine the normality of the distribution of data; an independent samples t-test was used to compare paired groups of normally distributed variables; the Mann-Whitney U test was used to compare paired groups of non-normally distributed variables, and chi-square and Fisher's exact tests were employed to compare the qualitative data. Logistic regression analysis was performed to determine the factors affecting mortality. A statistical significance of $p<0.05$ was considered significant.

RESULTS

Of the 365 patients, 162 (44%) were male and 233 (56%) were female. The mean age was 78.59±8.9 years in the BHA group and 80.38±8.74 years in the PFN group. There was no significant difference between the groups in terms of demographic characteristics ($p>0.05$)(Table 1). The length of hospital stay was 7.51±4.91 days in the BHA group and 7.08±7.93 days in the PFN group. The length of hospital stay was significantly longer in the BHA group compared to the PFN group ($p=0.013$). The ICU stay was 3.4±4.01 days in the BHA group and 3.11±5.89 days in the PFN group.

No significant difference was observed between the groups in terms of ICU stay (p=0.085). No significant difference existed between the groups in terms of time to surgery, ASA score, and intubation in ICU (p>0.05). The blood transfusion rate was 32/129 (24%) in the BHA group and 21/266 (7.8%) in the PFN group.

Table 1. Comparison of patients who underwent bipolar hemiarthroplasty with those who underwent proximal femoral nailing

		Arthroplasty (BHA) group n: 129		PFN group n: 266		p
Age	Mean±SD	78.59±8.98		80.38±8.74		0.059*
Laterality	Right	73	56.59%	153	57.52%	0.861+
	Left	56	43.41%	113	42.48%	
Sex	Male	52	40.31%	110	41.35%	0.843+
	Female	77	59.69%	156	58.65%	
Length of hospital stay (days)	Mean±SD	7.51±4.91		7.08±7.93		0.013†
	Median (IQR)	6 (4-10)		5 (4-8)		
Length of ICU stay (days)	Mean±SD	3.4±4.01		3.11±5.89		0.085†
	Median (IQR)	1 (-4)		1 (1-3)		
Time to surgery	First 24 hours	85	65.89%	162	60.90%	0.217+
	24-48 hours	23	17.83%	68	25.56%	
	After 48 hours	21	16.28%	36	13.53%	
ASA score	III	59	45.04%	125	46.99%	0.339+
	IV	70	54.26%	141	53.01%	
Intubation	No	115	89.15%	233	87.59%	0.655+
	Yes	14	10.85%	33	12.41%	
Blood transfusion	No	97	75.19%	245	92.11%	0.0001+
	Yes	32	24.81%	21	7.89%	
1-year mortality	Survived	94	72.87%	199	74.81%	0.496+
	Within 0-6 months	18	13.95%	42	15.79%	
	Within 6-12 months	17	13.18%	25	9.40%	
In-hospital mortality	Survived	119	92.25%	245	92.11%	0.961+
	Died	10	7.75%	21	7.89%	

BHA: Bipolar hemiarthroplasty, PFN: Proximal femoral nailing, SD: Standart deviation, ASA: American Society of Anesthesiologists, ICU: Intensive care unit, *: Independent t-test, †: Mann-Whitney U test, +: Chi-square test, †: Fisher's Exact test

The blood transfusion rate was significantly higher in the BHA group than in the PFN group (p=0.0001). The in-hospital mortality rate was 10/129 (7.7%) in the BHA group and 21/266 (7.8%) in the PFN group. There was no significant difference between the in-hospital mortality rates of the two groups (p=0.961).

The 1-year post-discharge mortality rate was 18/129 (13.9%) between 0-6 months and 17/129 (13.1%) between 6-12 months in the BHA group. The 1-year post-discharge mortality rate was 42/266 (15.7%) from 0-6 months and 25/266 (9.4%) from 6-12 months in the PFN group. There was no significant difference between the 1-year post-discharge mortality rates of the two groups (p=0.496).

The post-discharge mortality rate increased significantly with an advanced age (p=0.0001). The post-discharge mortality rates were significantly higher in patients with longer hospital stays, longer ICU stays, in patients with an ASA score of 4, intubated patients, and patients who received a blood transfusion. The post-discharge mortality rates were significantly higher in patients with comorbid congestive heart disease (CHF) (p=0.003), chronic obstructive pulmonary disease (COPD) (p=0.0001), and dementia (p=0.001) (Table 2).

Table 2. Evaluation of criteria that may affect mortality in discharged patients

		Survived n: 293		Died n: 71		p
Age	Mean±SD	78.82±8.87		83.51±8.19		0.0001*
Type of operation	Arthroplasty (BHA)	94	32.08%	25	35.21%	0.614+
	PFN	199	67.92%	46	64.79%	
Laterality	Right	156	53.24%	49	69.01%	0.330+
	Left	137	46.76%	22	30.99%	
Sex	Male	122	41.64%	25	35.21%	0.322+
	Female	171	58.36%	46	64.79%	
Length of hospital stay (days)	Mean±SD	5.84±3.74		10.2±10.34		0.0001†
	Median	5 (3-7)		7 (512)		
Length of ICU stay (days)	Mean±SD	2.06±2.40		5.00±7.77		0.0001†
	Median	1 (4-12)		3 (1-5)		
DM	No	251	85.67%	57	80.28%	0.259+
	Yes	42	14.33%	14	19.72%	
OP	No	290	98.98%	70	98.59%	0.780†
	Yes	3	1.02%	1	1.41%	
CAD	No	39	13.31%	9	12.68%	0.887+
	Yes	254	86.69%	62	87.32%	
HT	No	103	35.15%	21	29.58%	0.374+
	Yes	190	64.85%	50	70.42%	
CRF	No	290	98.98%	70	98.59%	0.780†
	Yes	3	1.02%	1	1.41%	
CHD	No	286	97.61%	64	90.14%	0.003+
	Yes	7	2.39%	7	9.86%	
COPD	No	227	77.47%	38	53.52%	0.0001+
	Yes	66	22.53%	33	46.48%	
Dementia	No	227	77.47%	41	57.75%	0.001+
	Yes	66	22.53%	30	42.25%	
CVA	No	278	94.88%	65	91.55%	0.280+
	Yes	15	5.12%	6	8.45%	
Malignancy	No	292	99.66%	70	98.59%	0.275†
	Yes	1	0.34%	1	1.41%	
Time to surgery	First 24 hours	202	68.94%	36	50.70%	0.002+
	24-48 hours	64	21.84%	19	26.76%	
	After 48 hours	27	9.22%	16	22.54%	
ASA score	III	169	57.68%	14	19.72%	0.0001+
	IV	124	42.32%	57	80.28%	
Intubation	No	291	99.32%	57	80.28%	0.0001+
	Yes	2	0.68%	14	19.72%	
Blood transfusion	No	267	91.13%	56	78.87%	0.003+
	Yes	26	8.87%	15	21.13%	

SD: Standart deviation, *Independent t-test; †Mann–Whitney U test; +Chi-square test; †Fisher's Exact test

Logistic regression analysis was performed with age, length of hospital stay (days) and ICU stay (days), CHF, COPD, dementia, time to surgery, intubation, blood transfusion, and ASA variables to determine the factors affecting in-hospital mortality. The length of ICU stay (days) (p=0.263), dementia (p=0.261), time to surgery (p=0.223), and blood transfusion (p=0.241) did not significantly affect in-hospital mortality; however, an advanced age (p=0.014), a longer length of hospital stay (days) (p=0.016), comorbid CHF (p=0.036) and COPD (p=0.021), intubation (p=0.0001), blood transfusion, and an ASA score of 4 (p=0.016) significantly affected in-hospital mortality (Table 3).

Table 3. Factors affecting in-hospital mortality		
Logistic regression analysis		
	or (95% CI)	**p**
Age	1.05 (1.03-1.09)	0.014
Length of hospital stay (days)	1.14 (1.03-1.27)	0.016
Length of ICU stay (days)	0.91 (0.77-1.08)	0.263
CHD	3.82 (1.09-8.41)	0.036
COPD	2.04 (1.07-3.89)	0.021
Dementia	1.56 (0.72-3.39)	0.261
Time to surgery		0.223
24-48 hours	0.76 (0.35-1.62)	0.472
After 48 hours	0.33 (0.09-1.17)	0.086
Intubation	7.43 (2.47-9.07)	0.0001
Blood transfusion	1.81 (0.67-4.90)	0.241
ASA IV	2.51 (1.19-5.30)	0.016

ICU: Intensive care unit, CHD: Coronary heart disease COPD: Chronic obstructive pulmonary disease, ASA: American Society of Anesthesiologists,

DISCUSSION

In this study, there was no significant difference between patients who underwent BHA and PFN for hip fractures in terms of in-hospital and 1-year post-discharge mortality rates. The 1-year post-discharge mortality rates were higher in patients with CHF, dementia, and COPD than in patients with other comorbid diseases.

In a study by Çelen et al.[11] comparing patients who underwent modular stem hemiarthroplasty with distal fixation and patients who underwent PFN for hip fractures, the 1-year mortality rate was 15.4% in the hemiarthroplasty group and 15.2% in the PFN group, resulting in no significant difference. In their study comparing patients who underwent BHA and PFN for hip fractures, Kılınç et al.[12] found a 1-year mortality rate of 26.8% in the BHA group and 23.9% in the PFN group, which also did not result in a significant difference. Durgut et al.[13] obtained comparable results in their study. Erkmen et al.[14] also found mortality rates to be similar between patients who underwent calcar-supported cemented BHA and those who underwent PFN. However, the authors found that post-operative, life-threatening complications were more common in the BHA group. In their study involving 618 patients, İpek et al.[15] found no difference between the 1-year survival rates of patients who underwent PFN and BHA. In the current study, the 1-year mortality rate was 26.1% in the BHA group and 25.2% in the PFN group. The difference was not significant.

However, the need for a blood transfusion and length of hospital stay were significantly higher in the BHA group compared to the PFN group. Thus, PFN is more advantageous in terms of blood transfusion requirements and length of hospital stay. In addition to the positive effect of less prolonged treatment for patients, PFN is also less costly. Similar results have been reported in previous studies.[15]

Pincus et al.[16] analyzed a cohort of 42,230 Canadians in terms of time from diagnosis to surgery. They reported that those who underwent surgery within 24 h of presenting with hip fractures had a lower 30-day mortality rate. In their study involving 2,056 patients operated on for hip fractures, Uzoigwe et al.[17] compared surgeries performed 36 h after admission with surgeries performed before the 36-h mark; the authors found that surgeries performed 36 h after admission resulted in higher post-operative mortality rates. An early systemic review of 16 published studies revealed that delaying surgeries for 48 h caused increased 30-day and 1-year post-operative mortality.[18] The results of previous meta-analysis studies by Simunovic et al.[19] support this finding. We also found that surgeries performed after 48 h result in a high post-discharge mortality rate but found no significant difference regarding in-hospital mortality.

In their multicenter study, McHugh et al.[20] determined that diabetes and dementia affected mortality in all processes, while COPD was the only disease associated with in-hospital mortality. In a study of 911 deceased patients, Barcelo et al.[21] found that 146 of them had CHF and 126 had dementia. We found that CHF, COPD, and dementia increased post-discharge mortality and that CHF and COPD increased in-hospital mortality. Therefore, appropriate pre-medication should be given, and follow-up should be strict for patients with cardiac and pulmonary pathologies due to their high rate of in-hospital mortality. The fact that dementia does not affect in-hospital mortality but affects post-discharge mortality suggests that although cognitive functions do not show their effect as rapidly as basic life functions, they have a negative impact in the long term.

The strengths of our study include the high number of patients and the homogenization of the patient groups by excluding patients with an ASA score of 2, patients <65 years of age, and patients who underwent revision surgery. The study has some limitations. The fact that it was retrospective and not randomized is an important limitation. In addition, although we were able to determine 1-year survival in the patients, it was not possible to determine long-term survival due to their age. Another limitation was that more than one surgeon operated on the patients. Other limitations are that the duration of the operations was not compared, and an objective parameter, such as the Harris Hip Score, was not used to evaluate hip function. One of the most significant limitations is that surgeries performed using PFN for pertrochanteric fractures and BHA for femoral neck fractures were compared. Although the fracture types compared occur in the same region, they are still different.

CONCLUSION

PFN for pertrochanteric fractures and BHA for femoral neck fractures are reliable surgical methods with good outcomes. There was no significant difference between the in-hospital and 1-year post-discharge mortality rates linked to the two surgical procedures. The PFN group had a shorter hospital stay and required less blood transfusion due to the minimally invasive method used. Patients with a longer time to surgery (>48 h), length of hospitalization and ICU stay, patients with an ASA score of 4, and intubated patients had higher 1-year post-discharge mortality rates. In addition, comorbid CHF, COPD, and dementia increased mortality rates. In-hospital mortality factors were age, length of hospital stay, intubation, an ASA score of 4, CHF, and COPD.

ETHICAL DECLARATIONS

Ethics Committee Approval
The study was carried out with the permission of University of Health Sciences Gazi Yaşargil Training and Research Hospital Clinical Researches Ethics Committee (Date: 13.01.2023, Decision No: 320).

Informed Consent
Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
The authors declared that this study has received no financial support.

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1476358
J Health Sci Med. 2024;7(3):332-336

The relationship of erectile dysfunction severity with nocturnal blood pressure pattern and RDW

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Cite this article as: Aslan M, Yavuz YE, Okşen D, Bal, E. The relationship of erectile dysfunction severity with nocturnal blood pressure pattern and RDW. *J Health Sci Med.* 2024;7(3):332-336.

Received: 30.04.2024 ◆ **Accepted**: 20.05.2024 ◆ **Published**: 27.05.2024

ABSTRACT

Aims: The study aimed to investigate the relationship between the severity of erectile dysfunction (ED), nocturnal blood pressure patterns, and red blood cell width distribution (RDW) in hypertensive patients.

Methods: The study involved 106 hypertensive patients, categorized into non-dippers and dippers based on their nocturnal blood pressure patterns. Key parameters including smoking status, RDW, and International Index of Erectile Function (IIEF) scores, were compared between the groups.

Results: The demographic data of the patients were similar. RDW was significantly higher in patients with non-dipper hypertension (HT) compared to the dipper group. Moderate and severe ED was seen more frequently in the non-dipper HT group (40.4% vs 20.4%; p=0.025). IIEF score was higher in the dipper HT group (17.6±6.9 vs 21.0±4.5; p=0.004). According to logistic regression analysis, age and smoking habit were significant predictors for moderate or severe ED.

Conclusion: The study highlights the significant association between non-dipping blood pressure patterns, elevated RDW, and the severity of ED in hypertensive patients. The findings underscore the importance of monitoring nocturnal blood pressure patterns and RDW in understanding and managing ED in this population.

Keywords: Hypertension, erythrocyte indices, erectile dysfunction

INTRODUCTION

Erectile dysfunction (ED) is a common condition that affects male health and quality of life.[1,2] It has multiple causes, one of which is hypertension (HT), a common comorbidity. HT can contribute to ED by affecting vascular health. Another cause of ED is atherosclerosis, which can impair penile arterial blood flow.[3-5] Red blood cell width distribution (RDW) is an emerging area of interest that may provide insights into the relationship between ED and systemic vascular health.[6-7] Early diagnosis of any underlying medical conditions contributing to ED is crucial for successful treatment. This article explores the intricate connections between ED, HT, and RDW and how these factors interrelate and influence men's health.

HT is a common health issue in the general population.[8,9] There are different ways to diagnose HT, with ambulatory blood pressure monitoring (ABPM) being one of them. ABPM not only diagnoses HT but also provides information about the patient's nocturnal dipping pattern.[10] Non-dippers are those patients whose blood pressure does not fall by more than 10% at night, and they are at a higher risk of morbidity and mortality compared to dippers.[11] Non-dippers are associated with several cardiovascular and non-cardiovascular diseases. It has been suggested that hypertensive patients with a non-dipper profile may have impaired endothelial function.[12] It has been demonstrated in multiple studies that non-dippers have notably lower levels of endothelium-dependent vasodilation when compared to dippers, due to significantly lower levels of nitric oxide (NO) release.[13]

The International Index of Erectile Function (IIEF) is a score that measures the ability to achieve and maintain an erection. It consists of five questions and is commonly used in clinical trials due to its simplicity. The IIEF is an effective tool for diagnosing ED.[14-15]

RDW is a marker that indicates the destruction of red blood cells and ineffective erythropoiesis. It has prognostic value in various cardiovascular diseases, along with anemia.[16-19] While there are many studies on the relationship between RDW and non-dipping/dipping patterns, there is limited research available on the correlation between RDW values and erectile dysfunction.[20]

The study explores the relationships between ED, HT and RDW. We investigated the correlation between the nocturnal blood pressure dipping pattern in hypertensive patients and ED severity (measured by the International Index of Erectile Function, IIEF) and the potential links between ED, dipping pattern, and RDW values.

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METHODS

The study was carried out with the permission of Siirt University Ethics Committee (Date: 28.02.2024, Decision No: 2024/2/02/06). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was designed as a cross sectional observational study. We included 150 patients who referred our cardiology polyclinic between November 2022 and July 2023. This study consisted of male population. Our inclusion criterias are patients who are diagnosed with hypertension and above 18 years old. Exclusion criterias are; i) patients with uncontrolled hypertension which is described as his blood pressure >180/100 mmHg despite optimal antihypertensive treatment, ii) patients with uncontrolled type 1 and 2 diabetes mellitus, iii) patients who diagnosed with erectile dysfunction before admission to our clinic and have treatment for ED. The study was approved by the local ethics committee and written informed consent was obtained from all patients enrolled into the study. 44 patients were ruled out according to exclusion criterias. 106 patients were enrolled in this study.

The IIEF-5 score is a diagnostic tool used to assess erectile dysfunction. All patients filled IIEF score form for the evaluation of the ED presence and severity. IIEF score contains 5 question about ability and maintain penile erection. It is determined by the sum of ordinal responses to five items. The scoring range and corresponding levels of erectile dysfunction are as follows: a score between 22 to 25 indicates no erectile dysfunction; a score of 17 to 21 suggests mild erectile dysfunction; a score of 12 to 16 signifies mild to moderate erectile dysfunction; a score between 8 to 11 is indicative of moderate erectile dysfunction; and a score of 5 to 7 is associated with severe erectile dysfunction.

After the physical examination, if the patient's blood pressure >140/80 mmHg and have not been diagnosed with hypertension before, we take control measurement after 15-minute resting state, and if BP is still above 140/80 mmHg, we perform 24-hour ABPM on the patient. ABPM was performed directly on patients with a previous diagnosis of hypertension. Twenty-four-hour ambulatory BP and heart rate monitoring were performed. Heart rate, systolic blood pressure and diastolic blood pressure were recorded every 15 minutes in the day-time and 30 minutes at nigh-time (22:00-07:00 accepted as night). Patients' clinic BP and ABPM measurements were recorded respectively.

Complete blood count and routine biochemistry, including lipid profile, are taken from all patients. Patients' White blood count, red blood cell count, hemoglobin, hematocrit, RDW, platelet count, and creatinine measurements were recorded. Echocardiography Epiq 7 ultrasound system (Philips Medical Systems; Andover, MA). Basic echocardiographic parameters, left ventricular ejection fraction and valvular pathologies were evaluated in all patients included in our study.

Statistical Analysis

SPSS 20.0 was used for statistical analysis. Continuous variables were reported as mean±SD for parametric data and median (25-75%) for nonparametric data. Categorical variables were expressed as frequency and percentage (%). Data distribution was assessed using the Kolmogorov-Smirnov test. The study compared variables between groups using the Student's t-test. Normal distribution was observed for most variables, while the Mann-Whitney-U test was used for variables that didn't meet the normality assumption. Categorical variables were compared using chi-square test. Univariate and multivariate logistic regression models were used to identify independent predictors of ED. A significance level of P<0.05 was used for all statistical analyses.

RESULTS

The information about the groups involved in the study is presented in Table 1. There was not any significant difference patients characteristics except smoking habits. Patients who had non-dipper HT smoked more frequently rather than dipper group (48.1% vs 27.8%; p=0.031). Patients, who had non-dipper HT, had a higher RDW percentage (15.3±2.6 vs 14.0±1.4; p=0.001), lower IIEF score (17.6±6.9 vs 21.0±4.5; p=0.004) and more frequent moderate to severe ED (40.4% vs 20.4%; p=0.025) compared to dipper group.

Table 1. Basic demographic characteristics of patients

Variables	Non-dipper HT (n=52)	Dipper HT (n=54)	p-value
Age (years)	55.7±11.5	52.4±10.8	0.139
BMI (kg/m^2)	29.4±3.6	29.7±4.0	0.349
Smoker n(%)	25(48.1)	15(27.8)	0.031
Systolic blood pressure (mmHg)	139±18	136±16	0.485
Diastolic blood pressure (mmHg)	82±10	84±10	0.241
WBC (x10^3/ul)	8.5±2.3	8.3±2.3	0.545
HGB (g/dl)	14.5(13.1-15.8)	14.9(13.5-16.0)	0.222
PLT (10^3/ul)	250±62	265±66	0.208
Creatinine (mg/dl)	1.05±0.24	1.02±0.17	0.549
eGFR (ml/min)	83.7(69.2-95.6)	90.2(75.3-98.0)	0.263
Total cholesterol (mg/dl)	178±44	191±40	0.122
HDL (mg/dl)	47.7±15.1	51.5±12.5	0.164
LDL (mg/dl)	111±28	117±33	0.277
Triglyceride(mg/dl)	144(126-185)	136(98-184)	0.595
Neutrophil	5.4±1.9	5.0±1.8	0.271
Lymphocyte	2.4±0.8	2.5±0.7	0.463
RDW (%)	15.3±2.6	14.0±1.4	0.001
IIEF score	17.6±6.9	21.0±4.5	0.004
Moderate-severe ED n(%)	21(40.4)	11(20.4)	0.025

BMI: Body mass index, eGFR: Estimate glomerular filtration rate, HDL: High density lipoprotein, LDL: Low density lipoprotein, RDW: Red cell distribution width, IIEF: International Index of Erectile Function, ED: Erectile dysfunction

According to multivariate logistic regression analysis models, smoking (OR:3.27, p:0.021) and age (OR:1.09, p:0.001) were independent predictors of moderate to severe ED (Table 2).

Table 2. Independent predictors of moderate-severe ED in patients in a univariate and multivariate logistic regression analysis model

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Age	1.103	1.051-1.158	<0.001	1.094	1.038-1.154	0.001
Non-dipper HT	2.648	1.117-6.279	0.027	1.980	0.714-5.491	0.189
Smoking	3.039	1.288-7.168	0.011	3.266	1.194-8.934	0.021
RDW (%)	1.000	0.999-1.000	0.036	1.000	1.000-1.000	0.329

ED: Erectile dysfunction, OR: Odds ratio, CI: Confident interval, RDW: Red blood cell width distribution

DISCUSSION

The findings suggests a strong association between non-dipping blood pressure patterns in hypertensive patients and increased prevalence of ED. Smoking status and higher RDW values were found significantly associated with ED. The study underscores the importance of considering nocturnal blood pressure patterns and RDW values in the clinical evaluation of ED in hypertensive patients. These results highlight the multifactorial nature of ED, emphasizing the need for a comprehensive approach to its diagnosis and management, especially in hypertensive patients.

The relationship between hypertension, specifically non-dipper hypertension HT, high RDW and ED is complex and multifaceted. Non-dipper HT is characterized by a diminished nocturnal decrease in blood pressure, leading to sustained high blood pressure that can impair vascular health. This impairment is crucial in the context of ED, as erectile function relies heavily on vascular integrity and blood flow.[21,22] In previous studies, it has been shown that Non-dipper HT adversely affects sleep quality.[23] This is known to be a factor that increases the risk of ED. The sustained high blood pressure in non-dippers can damage the vascular endothelium, reducing nitric oxide availability, a key mediator in erectile function.[24] In a previous study, it was shown that the IIEF score was higher in dipper HT patients than in non-dipper hypertensive patients.[25] Similarly, the study by Yildirim et al.[26] found that the severity of ED in newly diagnosed hypertensive patients is associated with the nondipper pattern, establishing nondipper HT as an independent predictor of ED. The study by Yuvanç et al.[27] investigated the effects of Nebivolol on ED in patients with nondipper hypertension, showing a significant improvement in ED according to the International Index of Erectile Function (IIEF) scores before and after treatment in the nondipper group. Another study by Yuvanç et al.[28] examined the effects of nocturnal blood pressure patterns on ED functions and found that nondipper hypertensive patients are more prone to developing ED. These findings underscore the significant role of the nondipper pattern in the relationship between cardiovascular risk factors and ED.

The study by Ateş et al.[29] investigated the relationship between masked arterial hypertension and ED, demonstrating that the nondipper pattern increases the risk of ED. Finally, the study by Kumaran et al.[30] examined the relationship between nocturnal systolic blood pressure patterns and ED in type 2 diabetic hypertensive men, showing that the nondipper status increases the risk of ED. In our study, it was consistent with previous studies (Figure 1). In addition, medium-high ED scores were significantly higher in non-dipper patients. However, in the multivariate logistic regression analysis, non-dipper HT may not have an independent effect on the risk of ED. Our study confirms these associations and provides new insights into the interplay between these factors in hypertensive patients. Our study extends these findings by demonstrating that patients with non-dipper HT not only have higher ED severity but also exhibit significantly higher RDW levels compared to dipper HT patients. This underscores the importance of RDW as a potential marker for vascular health and its role in ED pathophysiology.

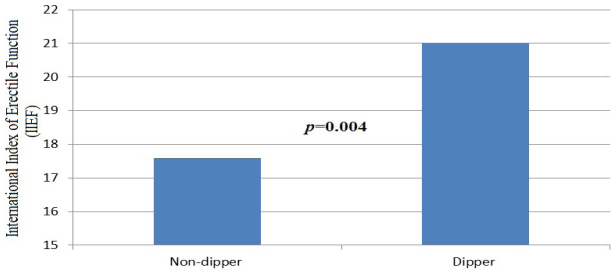

Figure 1. IIEF score distribution in Dipper and Non-Dipper HT patients

On the other hand, high RDW rates are indicative of anisocytosis (variation in RBC sizes), which is often a marker of systemic inflammation and oxidative stress.[31] These conditions are known to contribute to endothelial dysfunction, a common pathway in both cardiovascular diseases and ED. RDW, an independent prognostic marker in heart failure patients, has gained significant interest in current clinical practice.[32] It is associated with atherosclerosis and the presence and severity of CAD.[33] Moreover, a positive correlation between RDW level and cardiovascular events in CAD patients has been reported.[34] Elevated RDW levels may reflect a broader state of vascular pathology that could exacerbate the effects of hypertension on erectile function. In one study, a strong significant relationship was found between ED and RDW, and it was shown that there may be a prognostic value in diagnosis. A previous study comparing normotensive patients and non-dipper HT patients showed that RDW was significantly higher in non-dipping HT patients than in normotensive patients.[35] Our study corroborates these findings by showing a strong association between higher RDW values and ED severity in non-dipper HT patients (Figure 2). This highlights the potential of RDW as a prognostic marker for ED and its utility in clinical practice. A unique contribution of our study is the simultaneous evaluation of both RDW and the International Index of Erectile Function (IIEF) scores in hypertensive patients. While previous studies have examined these factors independently, our research provides a comprehensive understanding of their combined effects on ED. This dual assessment offers deeper insights into the interaction between cardiovascular and erectile health, emphasizing the multifactorial nature of ED in hypertensive

patients. Also in our study, unlike the literature, multivariate logistic regression analysis shows that RDW does not have a significant effect on the risk of intermediate- and high-risk ED.

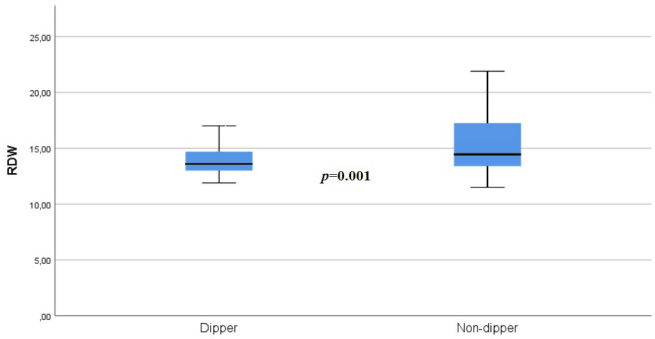

Figure 2. Relationship of Dipper and Non-Dipper HT groups to RDW

The statistical significance of the findings in this study, particularly regarding RDW and non-dipper HT, underscores their potential importance in the pathophysiology of ED. The strong association between higher RDW values and non-dipper blood pressure pattern in ED patients suggests that these parameters could serve as indicators of vascular health and erectile function. This insight is crucial for clinicians, as it highlights the need for comprehensive cardiovascular evaluation in ED patients, particularly those with hypertension. Additionally, these results pave the way for further research into targeted therapies that address these specific physiological mechanisms, potentially leading to more effective management of ED in hypertensive patients.

Limitations

Although univariate and multivariate logistic regression analyses are used, the selection of variables used in the analyses and the inclusion criteria of the patients may have an impact on the results. In this study, the independent effects of specific factors such as non-dipper HT and RDW on moderated-severe ED were investigated. However, the loss of significance of non-dipper HT in multivariate analysis may lead to the oversight of the effect of other non-included variables. This may be due to insufficient sample size or high variance in the data set. Studies of larger and more heterogeneous populations could improve the accuracy and reliability of these findings.

CONCLUSION

The study highlights the significant association between non-dipping blood pressure pattern, elevated RDW, and the severity of ED in hypertensive patients. However, this study's simultaneous evaluation of both IIEF and RDW provides a more comprehensive understanding of their combined effects on erectile dysfunction, increasing the depth of our insights into the interaction of cardiovascular and erectile health in hypertensive individuals.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Siirt University Ethics Committee (Date: 28.02.2024, Decision No: 2024/2/02/06).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1438190
J Health Sci Med. 2024;7(3):337-340

Relationship between pelvic floor complaints and multi-compartment prolapsus

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Cite this article as: Altıntaş T, Arslan Ç. Relationship between pelvic floor complaints and multi-compartment prolapsus. *J Health Sci Med.* 2024;7(3):337-340.

Received: 17.04.2024 ◆ **Accepted**: 12.05.2024 ◆ **Published**: 27.05.2024

ABSTRACT

Aims: The aim of this study is to investigate the frequency and characteristics of multi-compartment prolapse in women evaluated with pelvic floor complaints.

Methods: The data of 259 patients who applied to our hospital with pelvic floor complaints between May 2022 and March 2023 were evaluated retrospectively, and after the exclusion criteria were applied, the remaining 69 patients were included. Patients were grouped according to their primary complaints as those presenting with anterior compartment symptoms (ACS), those presenting with middle compartment symptoms (MCS), those presenting with posterior compartment symptoms (PCS), those presenting with proctological symptoms (PS) and those presenting with chronic pelvic pain (CPP).

Results: A total of 69 patients were included in the study. The mean age was 49.8±13.1 years and the median symptom duration was 60 months. When patients are evaluated in terms of main complaint; The primary complaint was ACS in 16 patients, MCS in 4 patients, PCS in 26 patients, PS in 20 patients, and CPP in 3 patients. According to MRI defecography findings, ACS was detected in 1 patients, MCS in 1 patients, PCS in 13 patients and multicompartment prolapse in 54 patients. In patients with a history of vaginal delivery, in patients with a history of previous pelvic surgery and as the number of vaginal delivery increases multi-compartment prolapse rate was significantly increased.

Conclusion: Regardless of the underlying primary complaint, the presence of multicompartment prolapse should be investigated through examination and tests in pelvic floor diseases. History and number of vaginal deliveries, previous pelvic surgery history carry a higher risk for multi-compartment prolapse.

Keywords: Pelvic floor, multi-compartment prolapse, pelvic organ prolapse, MRI defecography, rectocele, rectal prolapse, uterovaginal prolapse, cystocele

INTRODUCTION

Pelvic organ prolapse (POP) can be defined as the abnormal descent of the pelvic organs from their original location in the pelvis. POP is a serious health problem characterized by fecal or urinary incontinence, constipation, pelvic pain, vaginal pressure sensation and sexual dysfunction, affecting the quality of life and psychological state of patients. Although gynecologists commonly focus on uterine prolapse and vaginal problems, urologists focus on urinary symptoms and colorectal surgeons evaluate the issue focusing only on bowel dysfunction and posterior compartment prolapse, pelvic floor diseases are actually a group of diseases that require a multidisciplinary approach, with low treatment success and patient satisfaction when handled as a single-focused event.[1-3] POP is an important health problem affecting 41% of women worldwide.[4]

The pelvic floor consists of three anatomical compartments: anterior or urinary compartment (bladder and urethra), middle or genital compartment (vagina, cervix and uterus), and posterior or anal compartment (rectum and anus).[5]

To diagnose POP, the relationship of certain reference structures from each compartment to the pubococcygeal line (PCL) must be evaluated. PCL is obtained by drawing a line from the lower border of the symphysis pubis to the last coccygeal joint in dynamic Magnetic resonance imaging (MRI). PCL determines the pelvic floor level and POP is measured by drawing a line perpendicular to the PCL. The reference points for each compartment are the bladder base in the anterior compartment; posterior cervix or posterior fornix of the vagina in the middle compartment; and the anorectal junction in the posterior compartment. Severity of the prolapse can be graded using the 'rule of thirds'; Organ prolapse is mild if it is 3 cm or less below the PCL, moderate if it is between 3 and 6 cm, and serious if it is more than 6 cm.[6-8]

The most common anterior compartment syndrome (ACS) is cystocele, which causes complaints such as urinary incontinence, frequent urination, inability to fully void urine, frequent urinary tract infections and hematuria, depending

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on the degree of cystocele. When evaluating patients, the presence of simultaneous stress incontinence and urethral hypermobility should also be taken into consideration.[9]

Middle compartment syndrome pathologies are uterovaginal prolapses, peritoneocele, enterocele and sigmoidocele, and patients may present with complaints such as chronic pelvic pain, feeling of vaginal fullness, sexual dysfunction, constipation due to anorectal outlet obstruction, and feeling of insufficient defecation. The diagnosis of uterovaginal prolapse is usually made by clinical examination. Herniation of the pelvic peritoneal sac with fatty tissue into the rectovaginal space is called peritoneocele, if there is small intestines in the sac, it is called enterocele, and if there is a sigmoid colon, it is called sigmoidocele.[6]

Pathologies that cause posterior compartment syndrome are rectocele, rectal prolapse or rectal invagination, descending perineal syndrome, spastic pelvic floor syndrome (dyssynergistic defecation) and anal incontinence.

In this study, we wanted to evaluate the incidence of multicompartment prolapse, etiological factors and symptom characteristics in female patients with pelvic floor complaints.

METHODS

Ethics

Ethics committee approval was obtained from İstanbul Medipol University Non-interventional Clinical Researches Ethics Committee (Date: 31.08.2023, Decision No: 728). Patient consent was not needed because of the retrospective nature of the study. This study was conducted in line with the ethical principles specified in the Declaration of Helsinki.

Patients and Methods

The data of 259 patients who applied to our hospital with pelvic floor complaints between May 2022 and March 2023 were evaluated retrospectively. Male patients, patients whose primary complaints involve 2 or more compartments, patients without MRI defecography, etiologies not accompanied by pelvic organ prolapse (POP) (radiation proctitis, low anterior resection syndrome, fecal incontinence unrelated to POP, neural tube defects, vaginismus and dyssynergic defecation) were excluded. A total of 69 patients were included in the study.

The patients were evaluated by a coloproctologist and physiotherapist. When necessary, gynecology and urology consultations were requested on a patient basis. A detailed history was taken from the patients. Demographic data including age, parity, body mass index (BMI), previous prolapse and urinary incontinence surgeries were collected. The severity of symptoms and the quality of life were evaluated with the pelvic floor distress inventory (PFDI-20), pelvic floor impact questionnaire (PFIQ-7), and Cleveland Clinic Incontinence score (CCIS).[10] Patients were grouped according to their primary complaints as those presenting with anterior compartment symptoms (ACS), those presenting with middle compartment symptoms (MCS), those presenting with posterior compartment symptoms (PCS), those presenting with proctological symptoms (PS) and those presenting with chronic pelvic pain (CPP). All patients underwent pelvic and rectal examination and MRI/conventional defecography. Prolapse in more than one compartment on MRI defecography was considered as multi-compartment prolapse. Anal physiological examination, endoanal ultrasonography, urodynamics and colonoscopy were performed on patients when necessary. The presence of other accompanying compartment prolapse in each group was recorded according to MRI/conventional defecography evaluation. When necessary, patients were consulted by gynecology and urology departments.

Statistical Analysis

Statistical analyses were performed by IBM SPSS for Windows v.26 (SPSS, Statistical Package for Social Sciences, IBM Inc., Armonk, NY, USA). The distribution of the data was evaluated using histograms. Variables that were normally distributed were reported as mean and standard deviation and means were compared by independent sample t test, while skewed variables were reported as median, and range and means were compared by Mann-Whitney-U test. Chi-square test was used to compare differences between groups. p values <0.05 were defined as statistically significant.

RESULTS

A total of 69 patients with predominantly single compartment complaints were included in the analysis. The mean age was 49.8±13.1 years and the median symptom duration was 60 (1-480) months. The demographic characteristics of our patients are listed in Table 1. The average body mass index (BMI) is 25.5±5.2 and it is within normal limits. 75.4% of our patients had an average of 1.8 vaginal deliveries. 40.6% had a history of previous pelvic surgery such as hysterectomy, sacrocolpopexy, trans obturator tape (TOT).

Table 1. Demographic characteristics of the patients, pelvic floor complaints and MRI findings

Age (years, mean±SD)	49.8±13.1
BMI (kg/m^2, mean±SD)	25.5±5.2
Smoking status (+) (n, %)	26 (37.7%)
Comorbidity (+) (n, %)	30 (43.5%)
Menopausal status	**n (%)**
Premenopausal	31 (44.9%)
Postmenopausal	38 (55.1%)
History of vaginal delivery (+)	52 (75.4%)
Number of vaginal deliveries (mean±SD)	1.8±1.3
History of pelvic surgery (+)	28 (40.6%)
Symptom duration (months, median)	60 (1-480)
Complaints	**n (%)**
Anterior compartment	16 (23.2%)
Middle compartment	4 (5.8%)
Posterior compartment	26 (37.7%)
Proctological	20 (29%)
Chronic pelvic pain	3 (4.3%)
MRI defecography findings	**n (%)**
Anterior compartment prolapse	1 (1.4%)
Middle compartment prolapse	1 (1.4%)
Posterior compartment prolapse	13 (18.9%)
Multicompartment prolapse	54 (78.3%)

MRI: Magnetic resonance imaging, SD: Standart deviation, BMI: Body mass index

When patients are evaluated in terms of main complaint; The primary complaint was ACS (23.2%) in 16 patients, MCS (5.8%) in 4 patients, PCS (37.7%) in 26 patients, PS (29%) in 20 patients, and CPP (4.3%) in 3 patients. According to MRI defecography findings, ACS was detected in 1 patients (1.4%), MCS in 1 patients (1.4%), PCS in 13 patients (18.9%), and multicompartment prolapse in 54 (78.3%) patients. (Table 1).

Multi-compartment prolapse was detected most common in patients presenting with MCS complaints (n=4/4, 100%), followed by PCS (n=21/26, 80.8%), ACS (n=12/16, 75%), PS (n=15/20, 75%) and CPP (n=2/3, 66.7%) patients.

According to MRI defracography, single anterior compartment prolapse was detected in 1 patient and multi-compartment prolapse was detected in 22 patients (p=0.011). Middle compartment prolapse was detected as single compartment in 1 patient and as multi compartment in 3 patients (p=0.634). Posterior compartment prolapse was detected as single-compartment in 13 patients and as multi-compartment in 29 patients (p=0.570).

In patients with a history of vaginal delivery (83.3% vs 46.7%, p=0.007), in patients with a history of previous pelvic surgery (48.1% vs 13.3%, p=0.014) and as the number of vaginal delivery (1.9±1.3 vs 1±1.2, p=0.014) increases multi-compartment prolapse rate was significantly increased. In addition, the symptom duration was found to be 76.9±74.5 months in women with multi-compartment prolapse and 134.7±149 months in the group with single-compartment prolapse (p=0.049) (Table 2).

Table 2. Characteristics of single-compartment prolapse and multicompartment prolapse patients

	Multi-compartment prolapse status		
	No (n=15, 21.7%)	Yes (n=54, 78.3%)	p
Age (years, mean±SD)	48.6±16.3	50.2±12.3	0.672
BMI (kg/m^2, mean±SD)	23.5±2.6	26.1±5.8	0.481
Smoking status (+) (n, %)	6 (40%)	20 (37%)	0.531
Comorbidity (+)	31 (57.4%)	23 (42.6%)	0.502
Menopausal status	**n (%)**	**n (%)**	
Premenopausal	6 (40%)	25 (46.3%)	0.477
Postmenopausal	9 (60%)	29 (53.7%)	
History of vaginal delivery (+)	7 (46.7%)	45 (83.3%)	0.007
History of pelvic surgery (+)	2 (13.3%)	26 (48.1%)	0.014
Number of vaginal deliveries (mean±SD)	1±1.2	1.9±1.3	0.012
Symptom duration (months, median)	134.7±149	76.9±74.5	0.049
Complaints	**n (%)**	**n (%)**	
Anterior compartment	4 (25%)	12 (75%)	
Middle compartment	0	4 (100%)	
Posterior compartment	5 (19.2%)	21 (80.8%)	
Proctological	5 (25%)	15 (75%)	
Chronic pelvic pain	1 (33.3%)	2 (66.7%)	
MRI defecography findings	**n (%)**	**n (%)**	
Anterior compartment prolapse	1 (6.7%)	22 (40.7%)	0.011
Middle compartment prolapse	1 (6.7%)	3 (5.6%)	0.634
Posterior compartment prolapse	13 (86.6%)	29 (53.7%)	0.0570

SD: Standart deviation, BMI: Body mass index

DISCUSSION

When evaluating pelvic floor complaints, not only the patient's admission complaints at the outpatient clinic, but also the bladder complaints, sexual dysfunction, feeling of pressure in the pelvic floor, and bowel symptoms should be questioned in detail. In the anamnesis of the patient who applied with the complaint of pelvic floor disorder, accompanying comorbidities and risk factors such as diabetes, neuromuscular status, obesity, smoking and alcohol consumption, psychiatric status of the patient, menopause status, number of deliveries, previous surgeries and perineal lacerations including the anal sphincter should be evaluated before the surgical intervention.

In order to make a comprehensive systematic and standardized evaluation, evaluation can be made with the pelvic floor distress inventory (PFDI-20), pelvic floor impact questionnaire (PFIQ-7) and Cleveland Clinic Incontinence score (CCIS).[10] We evaluated the complaints of patients in our outpatient clinic using these scoring systems.

In our study, when we compared patients with and without multi-compartment prolapse, BMI was higher in the multicompartment group, but this was not statistically significant. Apart from this, age, comorbid diseases such as smoking, diabetes, coronary artery disease, hypertension and menopausal status were found to be similar between the two groups. The rate of vaginal delivery history and the number of deliveries were higher in the multi-compartment prolapse group, and this was found to be statistically significant. The rate of multicompartment prolapse was detected approximately 4 times more frequently in women with a history of previous pelvic surgery, and it was also statistically significant. Additionally, in our study, we found shorter duration of symptoms in women with multi-compartment prolapse. This can be interpreted as patients consulting a doctor earlier.

40% of women with vaginal prolapse have stress urinary incontinence (urinary incontinence with activity) and 37% have overactive bladder.[11] Additionally, postoperative stress urinary incontinence may occur in approximately 25% of women who undergo abdominal sacrocolpopexy surgery due to vaginal prolapse. This condition occurs as a result of opening the urethra and bladder neck after correction of anterior and apical vaginal prolapse. It may be possible to identify patients for whom prolapse repair and simultaneous prophylactic anti-incontinence surgery may be recommended.[12]

There are a limited number of studies in the literature reporting the results and morbidity rates of patients who underwent combined rectal and vaginal prolapse surgery. In a 2018 study using NSQIP data, 206 female patients who underwent rectopexy with sacrocolpopexy were compared with 3394 cases who underwent rectopexy alone from 2005 to 2014.[3] Overall morbidity did not differ significantly between groups (14.8% rectopexy alone versus 13.6% combined surgery, p=0.65). In a later NSQIP study on vaginal and rectal prolapse surgeries, 123 cases of simultaneous laparoscopic sacrocolpopexy and rectopexy performed between 2013 and 2016 were examined.[13] There was no statistically significant difference in complication rates between colpopexy,

rectopexy and simultaneous procedures (6.2, 7.6 and 8.9; p=0.058). Studies have shown that there is no difference in the complication rate between combined surgical procedures and single compartment surgery, and there is no reason for the surgeon to hesitate in this regard.

The degree of prolapse is determined by MRI/conventional defecography, and this examination is used to distinguish whether the prolapse is multicompartmental or accompanied by sigmoidocele, enterocele, or peritoneocele.

In our study, when 69 patients with single compartment complaints were evaluated with MRI defracography, it was determined that 54 patients had multiple compartment prolapse. In all three compartment complaints, the rate of detection of multicompartment prolapse is higher than the probability of detecting single compartment prolapse according to MRI defracography. Especially the association of anterior compartment prolapse with multicompartment prolapse is statistically significant. In addition prolapse was detected in all 3 compartments in all 4 women who presented with middle compartment complaints, but we did not perform a statistical analysis because the number was small.

CONCLUSION

As a result of our study, radiological prolapse was detected in patients without symptoms in the relevant compartment. As a result, when determining the diagnosis and treatment of a patient with a pelvic floor complaint, regardless of the underlying complaint, the patient should be investigated for multi-compartment prolapse through examination and tests. This may guide us in choosing the appropriate surgical procedure. Additionally, women who give birth vaginally and have a history of pelvic surgery should be examined more carefully for multi-compartment prolapse. We think that larger studies with longer follow-up periods are needed regarding the indication of treatment in these patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of İstanbul Medipol University Non-interventional Clinical Researches Ethics Committee (Date: 31.08.2023, Decision No: 728).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Data Availability

Data used in this study are included in the manuscript.

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Review

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1469966
J Health Sci Med. 2024;7(3):341-345

Exploring teledermatology in managing common inflammatory skin conditions: a systematic review

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Cite this article as: Gençoğlu Ş. Exploring teledermatology in managing common inflammatory skin conditions: a systematic review. *J Health Sci Med.* 2024;7(3):341-345.

Received: 17.04.2024 ◆ **Accepted**: 23.05.2024 ◆ **Published**: 27.05.2024

ABSTRACT

This investigation delves into the advancing domain of telemedicine within dermatology, highlighting its potential to reshape forthcoming healthcare paradigms. Specifically focusing on the utilization of teledermatology for prevalent inflammatory skin conditions, this study synthesizes literature comprising meta-analyses, comprehensive reviews, editor correspondences, real-world investigations, case collections, and detailed reports. Adhering to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards, manuscript selection and data extraction were meticulously executed. Initially, 121 relevant records were identified through database surveys. Following screening, 110 articles met the criteria for in-depth evaluation, with 92 articles ultimately included in our comprehensive review. Teledermatology, bolstered by the exigencies of the pandemic, emerges as a viable alternative for dermatological consultations in the foreseeable future. The rapid uptake and refinement observed during the crisis underscore its potential for further substantive advancements. Nonetheless, the establishment of structured guidelines governing its implementation and ongoing refinement remains imperative.

Keywords: Teledermatology, inflammatory skin conditions, telemedicine, healthcare dynamics, pandemic adaptation

INTRODUCTION

Defined by the World Health Organization (WHO), telemedicine encapsulates the utilization of information and communication technologies to deliver health care services when distance remains a pivotal factor. It encompasses diagnosis, treatment, prevention of diseases, research, evaluation, and continual education of health providers, all aimed towards enhancing the health of communities.[1]

Dermatology, alongside radiology and pathology, stands as one of the profoundly visual disciplines in medicine. The compatibility of these fields with telemedicine's modus operandi is evident through several studies accentuating the feasibility and reliability of such integrative approaches.[2,3] Notably, telemedicine often mirrors the diagnostic and management efficacy of in-person consultations.

While dermatology had previously acquainted itself with telemedicine,[2] its practicality was constrained due to limited applications, skepticism, and inexperience from both practitioners and patients.[4] The onset of the COVID-19 pandemic, however, drastically reshaped conventional paradigms. Mandated government interventions and lockdown protocols not only altered daily living but also necessitated a shift in clinical methodologies. Amidst this reshuffling, telemedicine re-emerged, not just as an alternative but as a vital armamentarium against the pandemic.[5]

In dermatological terrains, telemedicine assumed multifaceted roles: ensuring adherence to biologic treatments,[6] facilitating uninterrupted patient care, clarifying potential skin manifestations related to COVID-19,[7-9] and managing chronic inflammatory skin conditions.[10-15] This review delves into telemedicine's adaptability in dermatology during the COVID-19 onslaught, advocating its potential as the future's cornerstone.

METHODS

Literature for this study was culled from databases including PubMed, EBSCO, Embase, Google Scholar, Cochrane Skin, and MEDLINE (up to 20 September 2023). Search constructs combined terms like "SARS-CoV-2," "COVID-19," "telemedicine," "teledermatology," "skin manifestations," "acne," "psoriasis," and "hidradenitis suppurativa" among others. Adhering to the PRISMA guidelines, identified manuscripts underwent screening, extraction, and validation processes, visually summarized in Figure.

Inclusions were restricted to English-language manuscripts specifically addressing telemedicine's application in dermatology. Manuscripts exploring telemedicine outside dermatology or delving into other skin conditions (e.g., rosacea, skin cancers) were excluded.

Our focus spotlighted conditions including acne, psoriasis, atopic dermatitis, and hidradenitis suppurativa, reflecting the higher research density surrounding these diseases.

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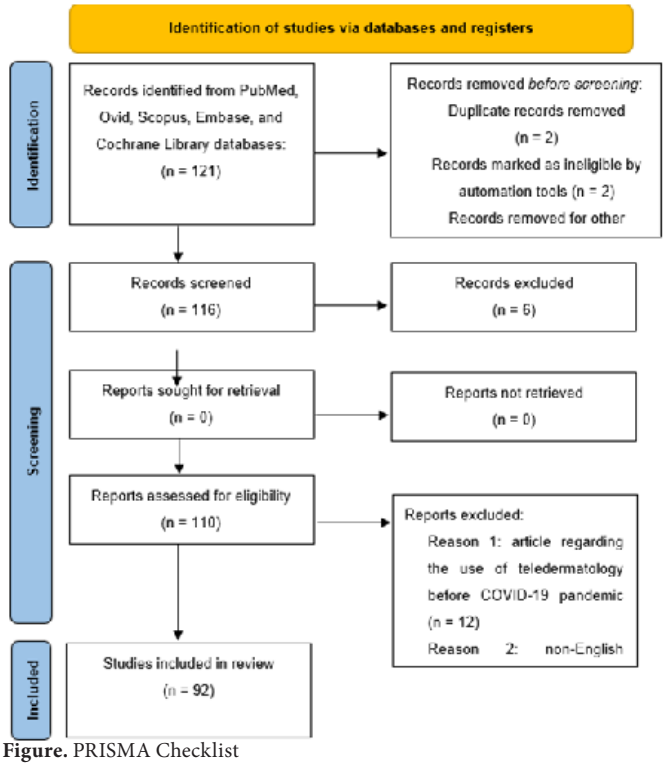

Figure. PRISMA Checklist

Gleaning from pre-existing studies, this article eschews primary human or animal research. Extracted data revolved around demographics, participant count, treatment strategies, and outcome measures, with DLQI as the primary outcome. A comprehensive risk bias evaluation, encompassing study methodologies, was performed by the author.

RESULTS

From the comprehensive database search, 121 records were culled. Post exclusion of duplicate and irrelevant articles, 110 were deemed eligible. Ultimately, after considering the inclusion and exclusion criteria, 92 articles were assimilated for this review. The focus predominantly hinged on chronic inflammatory skin disorders such as acne, psoriasis, atopic dermatitis, and hidradenitis suppurativa. These were emphasized not just due to their chronic nature, necessitating consistent follow-ups,[16-17] but also their substantial prevalence in the population.

Psoriasis

Affecting up to 3% of the global populace, psoriasis stands as a chronic inflammatory skin ailment mandating recurrent monitoring and sustained treatments to mitigate relapses. Particularly, the moderate to severe spectrum of the disease often necessitates systemic treatment with immunosuppressive or biologic agents.[18]

During the pandemic, telemedicine emerged as a lifeline for these patients, ensuring uninterrupted treatment regimes and monitoring potential treatment-related adversities.[19-20] In the context of psoriasis management during the pandemic, various studies were assessed:

One of the study underscored the indispensability of teledermatology, particularly in remote regions like the Faroe Islands, while also highlighting its selective application in urbanized regions.[21] Another of the study reported patients not only acclimatizing to online consultations but also showcasing a preference for them over traditional visits.[22] However, pinpointed the limited telemedicine adoption among the elderly, emphasizing the imminent need to make this platform more geriatric-friendly.[23] Studies also spotlighted clinicians' inclination towards telemedicine, resonating its pivotal role in curbing COVID-19 spread and concurrently economizing time and resources.[24] A substantial study encompassing 246 patients under biologics, revealed a 48% preference for teledermatology—underscoring its role in minimizing COVID-19 risk.[25] Another of study presented findings from 424 psoriasis patients consulting via phone calls, highlighting significant patient contentment.[26] One of the study explored telemedicine's psychological ramifications on psoriasis patients, concluding its mental health and depression outcomes were congruent with traditional visits. Conclusively, teledermatology has indisputably manifested as an efficient, reliable instrument in psoriasis management, ensuring therapeutic continuity during the pandemic. While enhancements are inevitable, the pandemic has accentuated the potential of telemedicine, advocating its permanency in future dermatological practices.[27]

Acne and Hidradenitis Suppurativa

Acne and hidradenitis suppurativa stand as predominant chronic inflammatory skin disorders impacting a vast spectrum of the population, with a consequent influence on life quality.[28]

Acne, which demands tailored therapies and consistent follow-ups, witnessed telemedicine as an indispensable tool during the COVID-19 era. Existing literature, even pre-pandemic, demonstrates teledermatology's effectiveness and safety for acne management.[29-30] Notably, Kazi et al.[31] showcased a significant patient preference for synchronous teledermatology for complex acne management. With isotretinoin prescription, topical drugs were more frequently advised than systemic ones, as evidenced.[32] Also delved into the feasibility of isotretinoin prescriptions and virtual visit modes, respectively. So that one of the study concluded a notable 50% patient preference for telematic services over conventional in-person visits.[33]

Hidradenitis suppurativa, however, presented unique challenges. Its affliction on intimate areas, like the groin, axillary, and scrotal regions, raised privacy concerns. The studies found a significant preference for in-person visits among patients, majorly due to discomfort in revealing intimate regions on camera. The literature suggested room for improvement in teledermatology privacy measures for such conditions.[34-36]

Atopic Dermatitis

Characterized by skin inflammation, redness, itching, and irritation, atopic dermatitis or atopic eczema affects a considerable portion of both children (up to 30%) and adults (up to 10%), severely impacting life quality.[37] The pandemic posed challenges for these patients requiring

regular specialist visits, especially those on biotechnological drugs. Telemedicine emerged as a vital solution.[38] The European Academy of Allergy and Atopic Dermatitis Clinical Immunology proposed telehealth's utility for various facets, from disease severity monitoring to medication reminders.[39] However, privacy concerns persist. Atopic patients, majorly children, raise concerns for parents who are wary of sharing their child's images on virtual platforms. Encrypted platforms ensuring secure image transmission are essential, especially given the frequent affliction of intimate regions in atopic dermatitis. In essence, while telemedicine emerged as a lifeline for various dermatological conditions during the pandemic, considerations of privacy, especially for conditions affecting intimate areas, must be prioritized.

CONCLUSION

In our examination, we started with the WHO's definition of telemedicine, which, in our perspective, encapsulates the core objectives of this discipline aptly. This modality gained pivotal importance amidst the COVID-19 pandemic, facilitating patient-doctor communication, bolstering preventive measures, and acting as a catalyst for ongoing medical training.

To conclude, telemedicine's prime contribution isn't limited to assisting patients with chronic skin inflammations; it's also pivotal in identifying dermatological repercussions post COVID-19 infection or vaccination. Numerous accounts attest to the onset or exacerbation of skin conditions related to these circumstances, emphasizing telemedicine's indispensable role in fostering patient assurance. Despite the pandemic waning, telemedicine's imprint on clinical practice remains indelible. Going forward, its utilization should be harmonized with universally recognized protocols and guidelines. Addressing privacy remains paramount; pursuing medico-legal avenues, like obtaining digitally-signed consents, might be the way forward. Lastly, an imperative need exists for platforms that marry superior image quality with user-friendliness, especially catering to the senior demographic.

Our study's foremost strength lies in its adherence to the PRISMA guidelines while reviewing contemporary literature. However, our approach also has certain limitations. We exclusively focused on teledermatology, excluding telemedicine's applications in other medical arenas. Additionally, we omitted studies examining teledermatology's role in managing other skin ailments beyond acne, hidradenitis suppurativa, psoriasis, and atopic dermatitis.

The global fight against the exponential spread of COVID-19 encompassed a slew of preventative strategies. Teledermatology emerged as a linchpin in this struggle. Our review accentuates the efficacy and safety of this modality but also underscores its inherent imperfections, which warrant rectification in ensuing years. We spotlighted the indispensable support this modality provided during the pandemic, particularly to patients grappling with chronic dermatological conditions such as psoriasis, atopic dermatitis, acne, and hidradenitis suppurativa. Not only were ongoing treatments unhindered, but patients also had the luxury of accessing medical consultations digitally when required, earning their commendation.

HIGHLIGHT KEY POINTS

Our analysis further draws attention to the challenges associated with this medium. The elderly demographic faced substantial hurdles navigating the various digital platforms, compounded by lapses in privacy protection, culminating in enhanced patient hardships. For teledermatology's long-term adoption, it's essential to ensure robust video consultation capabilities, which, in our opinion, holds an edge over conventional telephonic consultations. Our surveyed literature suggests that teledermatology excels more in follow-up consultations for patients already undergoing treatment, rather than inaugural sessions that risk diagnostic missteps. Future endeavors must focus on bolstering patient privacy, enhancing accessibility, and simplifying the user experience, especially for those less adept with digital tools. In summation, patients' overarching response to teledermatology has been overwhelmingly positive. Given the trajectory, telemedicine holds significant promise for the foreseeable future, especially if the challenges highlighted in our review are effectively addressed.

In the present context, teledermatology stands out as a promising avenue for dermatologists moving forward. The exigencies of the COVID-19 pandemic fast-tracked the evolution of digital medical services, embedding them deeper into daily clinical routines. As the echoes of the pandemic subside, we are confident that teledermatology's imprint will endure, given its demonstrated efficacy and safety credentials. Yet, further research is imperative to delineate its full potential, keeping in mind the constraints our manuscript highlights. Crafting comprehensive guidelines for teledermatology's application, coupled with relentless innovation, will chart the path for its future.

ETHICAL DECLARATIONS

Ethics Committee Approval
As this is a systematic review study, ethical committee approval is not required.

Referee Evaluation Process
Externally peer reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions
All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Review

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1462938
J Health Sci Med. 2024;7(3): 346-351

Obesity's cognitive consequences: leptin's influence on dementia

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Cite this article as: Kara E, Işıklı Ş. Obesity's cognitive consequences: leptin's influence on dementia. *J Health Sci Med.* 2024;7(3):346-351.

Received: 01.04.2024 ◆ **Accepted**: 15.05.2024 ◆ **Published**: 27.05.2024

ABSTRACT

Dementia is characterized by progressive cognitive decline and is increasingly associated with obesity. Obesity is identified by a number of pathological features, including excess fat accumulation, insulin resistance, gut dysbiosis, oxidative stress, inflammatory activation and systemic inflammation. These pathological factors trigger neuroinflammation and brain damage, making the complex relationship between metabolic health and cognitive function more salient. The amount of leptin in the bloodstream is correlated with the proportion of body fat and regulates cognitive processes as well as metabolic functions through its effects on the central nervous system. However, obesity can lead to leptin resistance, which may contribute to the development of neurodegenerative disorders such as dementia by impairing leptin's ability to maintain cognitive functions. This article discusses the gut-brain axis as a critical mediator of the effects of obesity on cognitive health and highlights the impact of gut dysbiosis on cognitive decline as a result of neuroinflammation. Obesity-specific systemic inflammation exacerbates neurodegeneration, increasing the need for integrated approaches to manage obesity and its cognitive repercussions. Addressing the pathological features of obesity by optimizing leptin signaling may offer promising strategies to prevent or slow the progression of cognitive decline associated with obesity and metabolic syndrome.

Keywords: Obesity, dementia, cognitive decline, leptin

INTRODUCTION

Dementia covers a range of conditions marked by severe and/or persistent cognitive decline, which significantly affects an individual's daily functioning and quality of life. This cognitive decline is manifested through deficits in one or more of six cognitive domains: language, memory, attention, social/emotional behavior, executive functioning, and visuospatial abilities. As a multifaceted disorder, dementia's etiology is affected by various factors, including aging, genetics, cardiovascular health, and metabolic conditions. With the global aging population, the prevalence of dementia is alarmingly projected to increase from roughly 57 million cases in 2019 to over 150 million by 2050, highlighting a growing public health concern.[1]

This dire projection emphasizes the critical necessity for a deeper understanding of dementia's pathophysiology and contributing risk factors to spur the development of effective treatments. Currently, the therapeutic landscape for dementia remains starkly limited, leaving many patients without effective options to manage their condition.

Obesity, rapidly emerging as a major contributing factor for dementia, presents a complex challenge in understanding and mitigating cognitive decline. Defined commonly through the body mass index (BMI), obesity reflects excessive adipose tissue accumulation, contributing to a myriad of health issues beyond cognitive health, including cardiovascular diseases and diabetes. Approximately 1.2 billion people worldwide are classified as overweight, with 650 million suffering from obesity, indicating a global health epidemic.[2]

The link between obesity and dementia is multifaceted, encompassing various pathological features beyond simple nutrient storage. Chronic, low-grade inflammation, a hallmark of obesity, along with adipose tissue hypertrophy, stimulates the release of pro-inflammatory mediators leading to oxidative stress and end-organ damage. These pathological features not only have systemic effects but also specifically impact brain health by compromising neurovascular connectivity, essential for delivering oxygen and nutrients to active neurons, thereby fostering conditions conducive to cognitive impairment and dementia.[3]

Moreover, obesity's impact on dementia risk varies across different life stages, with mid to late adulthood identified as critical periods for increased risk. This variability suggests that the timing and duration of obesity exposure may influence the trajectory of cognitive decline, highlighting the importance of early intervention and sustained health management across the lifespan.[4]

The gut-brain axis emerges as a critical pathway through which obesity may influence dementia risk. Altered gut microbiota, or dysbiosis, has been linked to increased neuroinflammation, a recognized characteristic of dementia.[5] The dynamic relationship between the gut and brain, mediated by neural, endocrine, metabolic, and immune pathways, offers potential therapeutic targets for mitigating cognitive decline through interventions aimed at restoring gut health balance.[6]

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Additionally, the role of adipokines, particularly leptin, in modulating cognitive health offers further insight into the obesity-dementia link. Leptin, known for its role in energy homeostasis and body weight regulation, also influences cognitive functions. However, obesity can lead to leptin resistance, undermining its protective effects on the brain and potentially contributing to the onset of neurodegenerative diseases like Alzheimer's disease (AD).[7,8]

The increasing amount of research associating obesity to chronic conditions like diabetes further complicates the relationship between metabolic health and cognitive function. Type 2 diabetes, often a consequence of obesity, has been closely linked to a higher risk of developing dementia, including AD. This association emphasizes the intertwined nature of metabolic and cognitive health, underscoring the need for integrated approaches to treatment and prevention.[9,10]

In light of these challenges, current research efforts are focused on identifying early markers of dementia, elucidating the mechanisms by which obesity contributes to cognitive decline, and exploring potential interventions. Addressing obesity through lifestyle modifications, targeted therapies, and interventions aimed at improving gut health could have a considerable impact on reducing dementia risk.[11]

In conclusion, the intersection of obesity, metabolic health, and dementia presents a complex challenge requiring a multifaceted approach to research, treatment, and prevention. Understanding the intricate pathways linking these conditions is crucial for developing effective strategies to alleviate the increasing burden of dementia. As the global population ages and obesity prevalence rises, the need for concerted efforts to address these interconnected health issues becomes increasingly urgent. Future research should proceed to explore the gut-brain axis, adipokine modulation, and the potential for lifestyle and therapeutic measures to prevent or invert the cognitive decline linked to obesity and metabolic syndrome, offering hope for those affected by dementia.

OBESITY AND DEMENTIA LINK

Obesity's link to dementia is increasingly evident, underscoring a complex interplay between excessive adipose tissue accumulation and cognitive decline. This condition, marked by chronic, low-grade inflammation and metabolic dysregulation, poses significant risks for both physical health and cognitive functions, contributing to the pathogenesis of dementia, including AD and vascular dementia.[12,13]

Recent research highlights the critical period of middle age as a major risk factor for the subsequent development of dementia. Studies indicate that a BMI exceeding 25 during this phase is related to an increased probability of cognitive decline in subsequent years.[14] Conversely, weight loss in later life, potentially due to malnutrition, also correlates with heightened dementia risk, suggesting the timing of obesity's impact plays a crucial role in cognitive outcomes.[15]

The pathological features of obesity, such as adipose tissue hypertrophy and the resultant systemic inflammation, compromise neurovascular connectivity, crucial for neuron function and health.[16] This impairment can initiate or exacerbate neuronal dysfunction, leading to cognitive impairments seen in various dementia forms. Notably, obesity in mid-life appears to set the stage for long-term brain damage, with the effects potentially becoming apparent only as dementia in later life.[17-19]

Obesity's role as a dementia risk factor is further complicated by its contribution to other neurodegenerative diseases, such as Parkinson's[20,21] and Huntington's diseases.[21,22] The mechanisms include alterations in brain structure, evidenced by reduced grey matter volume, and functional changes, such as impaired insulin signaling in the brain, which are central to obesity's impact on cognitive health.[23]

The measurement of adiposity through BMI, although widely used, has its limitations, prompting the use of other indices like waist circumference and waist-to-hip ratio (WHR) to assess fat accumulation.[23] These measures have shown that obesity's metabolic profile, including its association with grey matter volume reductions, could contribute to decreased cognitive functions.[23,24] Nevertheless, the association between obesity and dementia remains complex, with studies suggesting a possible U-shaped curve, where both low and high adiposity levels are linked with cognitive impairment.[25-31]

Animal studies have confirmed obesity's link with cognitive dysfunctions, demonstrating that diets rich in saturated fats can impair hippocampal-dependent learning and memory functions.[32,33] Furthermore, obesity-induced inflammation and insulin resistance are crucial factors that exacerbate neurodegeneration, underscoring the necessity of addressing obesity as part of dementia prevention and management strategies.[34]

In summary, the connection between obesity and dementia is multifaceted, involving direct impacts on brain health through systemic inflammation, metabolic dysfunction, and alterations in brain structure and function. As obesity remains to be a significant public health challenge, understanding its role in dementia is essential for developing preventive measures and therapeutic interventions aimed at mitigating cognitive decline associated with excessive adiposity.

PATHOLOGICAL FEATURES OF OBESITY

Obesity's pathological landscape is marked by several detrimental features, notably insulin resistance,[35] gut dysbiosis,[36] oxidative stress,[37] inflammatory activation,[38] and systemic inflammation.[16] Each plays a crucial role in the cascade leading to neuroinflammation and brain damage. Insulin resistance, a hallmark of obesity, exacerbates metabolic dysregulation and has been shown to contribute directly to neuroinflammation, setting the stage for neurodegeneration and cognitive dysfunction.[35] Clinical evidence suggests an association between insulin and leptin resistance and cognitive impairment and neuropsychiatric conditions. Interestingly, these studies suggest that deficits in neuroplasticity associated with these conditions may potentially be reversed by restoring insulin and leptin sensitivity.[39] This metabolic anomaly impacts the brain's insulin signaling, which is essential for cognitive function and neuronal health. There is evidence that leptin may be involved in AD. The decline in plasma leptin levels with age has been associated with an increased risk of cognitive decline and the potential onset of this condition.[40]

A recent study comparing leptin levels in lesions from psoriasis patients with and without multiple sclerosis (MS) found that leptin levels in psoriatic lesions were significantly higher in psoriasis patients with MS than in those without MS. This finding suggests that leptin may be a key molecule responsible for the poor response of psoriasis associated with MS.[41]

Gut dysbiosis in obesity further complicates this picture by disrupting equilibrium between beneficial and harmful bacteria in the gastrointestinal tract. This imbalance promotes a state of chronic inflammation and oxidative stress-conditions known to negatively impact brain health.[5] Elevated levels of hippocampal glutathione, a marker of oxidative stress, have been closely linked to increased risks for developing dementia, showcasing the direct impact of metabolic health on cognitive function.[42]

GUT-BRAIN AXIS

The gut-brain axis offers a critical pathway through which obesity influences cognitive health. This bidirectional communication network between the gut microbiota, the enteric nervous system (ENS), and the central nervous system (CNS) highlights the profound effect of gut-derived factors on brain function.[5] Dysbiosis, characterized by an imbalance in gut microbiota composition, triggers oxidative stress, thereby promoting neuroinflammation and paving the way for cognitive impairment.[43] The interplay between the gut and the brain during dysbiosis involves complex neural, endocrine, metabolic, and immune pathways, emphasizing the potential cognitive decline stemming from compromised gut health.[6] Furthermore, bacterial endotoxins can affect behavior and cognitive function by sending sensory inputs to the CNS via vagal afferent fibers, showcasing a direct link between gut health and brain function.[44] In addition, the gastrointestinal-brain axis releases several anorexigenic signals, including uroguanylin, glucagon-like peptide-1, amylin and cholecystokinin, which may mitigate resistance to the effects of leptin.[45]

SYSTEMIC INFLAMMATION

Systemic inflammation stands out as a critical consequence of obesity, significantly contributing to neuroinflammation. The expansion of adipose tissue leads to a hypoxic environment that triggers adipocyte apoptosis and elevates pro-inflammatory cytokines and adipokines such as TNF-α, leptin, and IL-6.[46] These molecules not only foster a systemic inflammatory state but are also recognized as key contributors to cognitive impairment.[17] The dysregulated adipokine release in obesity tips the balance towards a pro-inflammatory state, further exacerbating conditions like leptin resistance and increased blood-brain barrier (BBB) permeability. This pro-inflammatory milieu facilitates cerebral atrophy and compounds the risk of developing dementia.[47]

Understanding obesity's pathological features, the gut-brain axis's role, and the impact of systemic inflammation underscores the intricate relationship between obesity and cognitive decline, including dementia. Addressing obesity's multifaceted pathological impacts is crucial for developing effective strategies to mitigate the risk of dementia, highlighting the need for comprehensive approaches to manage obesity and its widespread effects on cognitive health.

OBESITY AND LEPTIN

Within the framework of obesity and it's association with health complications, leptin plays a pivotal role in maintaining energy homeostasis and body weight by orchestrating a network of signals among peptides secreted by various organs. This hormone, produced by adipocytes, exhibits pleiotropic effects across different tissues, significantly influencing physiological functions. Leptin's primary function in regulating appetite and energy expenditure positions it as a key player in the discussion on obesity and its linkage to dementia.[48,49]

Leptin levels in the bloodstream directly correlate with body fat mass, serving as an adiposity indicator.[50,51] These levels fluctuate due to factors such as gender, BMI, fasting states, and overall energy balance, and are subject to circadian rhythms, peaking between midnight and dawn. The leptin hormone is encoded by the obesity (ob) gene and interacts with class I cytokine receptors, specifically through its various isoforms.[52]

Among these isoforms, the long form (LepRb) is notable for its involvement in the activation of Janus kinase (JAK) and signal transducers and activators of transcription (STAT) signaling pathways, crucial for leptin's systemic effects. Leptin receptors are distributed widely, not only in the CNS across regions integral to hunger and satiety but also throughout the body. Their presence in brain microvessels suggests a role in transporting leptin throughout the BBB, highlighting the complexity of leptin's impact on the brain and its potential contribution to conditions like dementia.[53-57]

Biochemical interaction with the leptin receptor activates JAK2, which subsequently phosphorylates tyrosine residues to initiate several intracellular signaling pathways.[53,58,59] These pathways include the activation of STAT3 via JAK, the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway, extracellular signal-regulated kinases (ERK), and signal transducer and activator of transcription 5 (STAT5). Through these mechanisms, leptin influences cognition, neurogenesis, neuroprotection, synaptic plasticity, and structural brain changes, underscoring its significant yet complex role in the nexus between obesity and cognitive health.[60,61]

LEPTIN: COGNITION AND SYNAPTIC FUNCTION RELATIONSHIP

The intricate balance of body weight and energy homeostasis is critically maintained through a network of signals among peptides secreted by various organs, with adipocytes playing a central role through their secretion of adipokines. Among these, leptin stands out for its pivotal role in regulating food consumption and energy expenditure, highlighting its significance in the context of obesity and its potential implications for dementia.[62]

Leptin, proportional to body fat mass, serves as a key indicator

of adiposity, with its plasma levels subject to fluctuations based on gender, BMI, fasting states, and energy balances.[50,51] While leptin and body weight have been tightly controlled in previous studies, the effect of age has been a subject of curiosity. In a mouse study investigating the age-related satiety effect of leptin, exogenous leptin administration was found to have a transient effect in young male mice and to reduce food intake in older mice. Similarly, the lack of changes in leptin clearance from the blood and its transport to the brain suggests that a central resistance to leptin develops in middle age.[63] A study investigating sex differences in leptin found significant species differences in the development of diet-induced obesity between rats and mice; mice exhibited different food preference behaviour, glucose tolerance and energy expenditure compared to rats.[64]

On the other hand leptin follows a circadian rhythm, peaking at night, and is modulated by other hormonal and cytokine interactions.[52] Originating from the ob gene, leptin acts through its receptors, categorized as class I cytokine receptors, which are extensively present throughout the body, including significant areas within the CNS such as the hypothalamus and the hippocampus.[53,57,60,65-68]

The diversity of leptin receptors, including the long form LepRb crucial for JAK and STAT signaling, underpins the hormone's broad physiological effects. These effects extend beyond metabolic regulation, encompassing roles in cognition, neurogenesis, and synaptic plasticity. The engagement of leptin with hippocampal glutamate receptors underscores its involvement in synaptic transmission, crucial for learning and memory processes. This relationship is evidenced by leptin's ability to enhance long-term potentiation (LTP) and rectify long-term depression (LTD), with deficiencies in leptin signaling leading to cognitive impairments.[55,59,69]

LEPTIN RESISTANCE: MECHANISMS INVOLVED

Leptin resistance, a paradox of elevated leptin levels without the expected physiological response of satiety in obesity, presents a significant challenge.[69,70] This resistance within the hypothalamus, despite high circulating levels, points to a breakdown in leptin signaling mechanisms.[66] Factors contributing to leptin resistance include genetic predispositions, alterations in BBB transport, receptor desensitization, and a myriad of inflammatory processes that disrupt leptin's signaling pathways. These factors not only perpetuate the cycle of obesity but may also predispose individuals to cognitive decline and dementia by disrupting the homeostatic and cognitive functions regulated by leptin.[58,70]

In the context of dementia, leptin's neuroprotective roles are of particular interest. Based on an in vivo human study, the results suggest that maintaining adequate plasma leptin levels may be protective against the development or progression of AD pathology, including both amyloid-beta (Aβ) and tau deposition. Therefore, more attention needs to be paid to the role of leptin in the prevention of AD and related cognitive impairment in older adults.[71] Leptin's involvement in neurogenesis, synaptogenesis, and neuronal excitability offers potential pathways through which leptin resistance may contribute to cognitive decline.[62,72] The evidence of leptin enhancing cognitive functions in animal models of AD further supports its potential as a target for therapeutic intervention.

Furthermore, the U-shaped correlation between circulating leptin levels and cognitive performance suggests that both deficiency and excess of leptin could be detrimental to cognitive health. This underscores the need for a balanced leptin signaling mechanism for optimal cognitive functioning.[38,73]

In conclusion, the roles of leptin in energy homeostasis, cognitive functions, and the phenomenon of leptin resistance offer insightful perspectives into the complex interplay between obesity and cognitive health.[48,49,74] Addressing leptin resistance and exploring strategies to optimize leptin signaling could provide promising avenues for mitigating obesity-related cognitive decline and enhancing overall brain health.

CONCLUSION

The complex relationship between obesity and dementia is marked by intertwined metabolic, inflammatory, and neuroendocrine pathways, which collectively contribute to cognitive decline. Chronic inflammation and metabolic dysregulation, particularly manifesting as leptin resistance, are central to this association, emphasizing the need for multifaceted intervention strategies. The gut-brain axis and systemic inflammation play pivotal roles in linking obesity with neurodegenerative processes, suggesting that targeted interventions in these areas could help mitigate dementia risk.

Understanding the dual role of leptin in energy regulation and cognitive processes offers potential therapeutic targets to counteract obesity-induced cognitive impairments. An integrated approach combining dietary, behavioral, and pharmacological strategies is essential for maintaining metabolic health and cognitive function. Future research should focus on elucidating the underlying mechanisms of the obesity-dementia connection, identifying early disease biomarkers, and developing interventions to address the complex interactions involved.

By advancing our understanding and treatment of obesity-related cognitive decline, we can aim to lessen the dementia burden, improving life quality and cognitive health for the aging population worldwide.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Case Report

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1454888
J Health Sci Med. 2024;7(3):352-355

Resin infiltration applications in white spot lesions with caries cavities

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Cite this article as: Karaduran B, Tuna İnce EB, Koruyucu M. Resin infiltration applications in white spot lesions with caries cavities. *J Health Sci Med.* 2024;7(3):352-355.

Received: 18.03.2024 ◆ **Accepted**: 03.04.2024 ◆ **Published**: 27.05.2024

ABSTRACT

White spot lesions (WSLs) describe the initial stage of caries and appear more opaque and white than normal enamel due to changes in the refractive index of light compared to the normal enamel structure. This condition can cause aesthetic concerns for the patient. The primary cause of its formation is poor oral hygiene and excessive plaque accumulation. In the approach to treatment, significant innovations have occurred over time, and the principle of preserving the tooth structure as much as possible has been adopted instead of removing dental tissue and make restoration. The resin infiltration (RI) technique is believed to reduce the amount of dental tissue that needs to be removed in the treatment of WSLs with cavitated carious lesions while meeting the patient's aesthetic expectations. This present case report describes the application and follow-up of the RI technique in pediatric patients with cavitated carious lesions adjacent to WSLs in maxillary anterior teeth. Following RI treatment according to the recommendations of the manufacturer, composite restoration was applied to the teeth deemed necessary for restoration, in two male patients aged 14 and 8, who presented with caries cavities.

Keywords: Caries, resin infiltration technique, white spot lesions

INTRODUCTION

In the initial stage of caries formation, the opaque and white-colored demineralization areas on or beneath the enamel surface are referred to as white spot lesions (WSL).[1,2] In the early stages, WSLs appear more opaque and white than normal due to a porous structure in the lesion body, while the surface initially remains intact, causing a change in the light refractive index. The primary cause of WSL formation is often demineralization resulting from poor oral hygiene. Although commonly observed after orthodontic treatment, WSLs frequently occur in the cervical area adjacent to the gingiva and on the vestibular surface of the tooth in patients with poor oral hygiene. It is noted that WSLs could start to develop within a short period, approximately 1 month, after the placement of brackets in orthodontic treatment, but the formation of cavitation requires a longer period, around 6 months.[3-6] Risk factors may include poor oral hygiene, altered saliva flow, and the presence or absence of fluoride.[6-8]

In the treatment of WSL, the goal should be to stop demineralization while also supporting remineralization. While the conventional treatment approach involves removing demineralized tooth structure and performing restoration, the importance of minimal invasive (MI) treatment procedures has increased to preserve dental structure as much as possible.[7] For these reasons, the use of various fluoride-containing preparations and topical applications, agents supporting remineralization such as casein phosphopeptide-amorphous calcium phosphate (CPP-ACP), xylitol, hydroxyapatite, tricalcium phosphate, the use of resin infiltration (RI) technique, and the application of 18% hydrochloric acid (HCl) with microabrasion are considered as primary treatment preferences in the MI approach for WSL treatment.[7,8]

The RI technique may be considered more advantageous due to the potential disadvantages of many topically applied agents among the mentioned treatment options. These disadvantages include the need for long-term patient cooperation, delayed results, and the risk of the remineralizing powwer being limited to the outer surface of the enamel only.[8] There is limited evidence in the literature regarding the combined application and evaluation of RI and composite restoration in the treatment of WSL with caries cavities. The purpose of this study is to present cases evaluating the effectiveness of RI technique in conjunction with composite restoration material in the treatment of WSLs adjacent to caries cavities in children with poor oral hygiene. In both cases, detailed information was provided to the patient and their family, and signed consent forms were obtained before the treatment.

CASE 1

The 14-year-old male patient and his family, with no significant medical history, complaint aesthetic concerns about the appearance of WSLs on the vestibular surface of the maxillary anterior teeth. Periodontal prophylaxis was administered, and guidance on oral hygiene was provided

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in the first session. After isolation using rubber dam and dental floss, ICON® (DMG, Hamburg, Germany) application was decided for WSLs on teeth 11, 12, 13, 14, 21, 22, 23, and composite restoration was planned for teeth 12 and 23, where cavitation was detected at the beginning of the treatment at the next session. Following the application of ICON-Etch containing 15% HCl acid for 2 minutes and ICON-Dry with 30 seconds of ethanol rinse according to the manufacturer's recommendations. Acid application was repeated three times in total based on this examination. Then, ICON-Infiltrant containing tetraethylene glycol dimethacrylate (TEGDMA) was applied to the vestibular surfaces of the specified teeth, waiting for 3 minutes, and polymerized with Elipar DeepCure-S Light Device (3M Oral Care, St. Paul, USA) for 40 seconds. Another one minute of ICON-Infiltrant application followed by 40 seconds of light curing was performed, and it was noted that the white spot lesions (WSL) disappeared. It was determined that there was no need for composite restoration on tooth 12. To make a better assessment of the need for composite restoration on all teeth, the patient was recalled two days later, and it was decided to perform composite restoration only on tooth 23. G-Premio universal bond (GC Corp., Tokyo, Japan) was used as the adhesive agent, and G-aenial anterior (GC Corp., Tokyo, Japan) A2-colored composite was applied according to the manufacturer's recommendations (Figure 1).

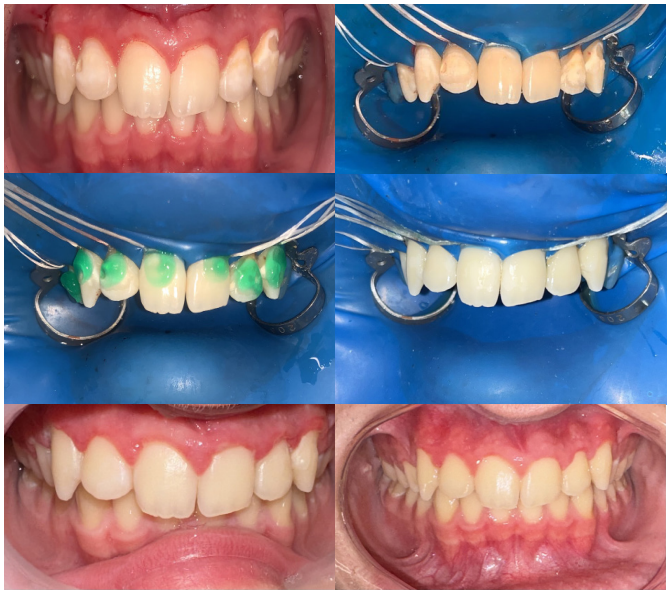

Figure 1. Treatment pictures for Case 1. (a) Initial intraoral view, (b) Intraoral view after applying rubber dam, (c) ICON-Etch application, (d) View after applying ICON-Infiltrant, (e) Intraoral view after removing rubber dam, (f) Intraoral view after composite restoration on the vestibulocervical of tooth 23

CASE 2

An 8-year-old male patient without any medical conditions and his family visited our clinic due to general dental examination and concern about the appearance of his maxillary anterior teeth. It was decided to apply ICON® to teeth 11, 12, 21, 22, and to restore the interproximal caries lesions of teeth 11 and 21 with composite. The teeth were isolated using rubber dam and dental floss. ICON-Etch was applied to the WSLs on the isolated teeth for 2 minutes, and after rinsing with water, visual assessment of the lesions was performed using ICON-Dry after 30 seconds of its application. Based on these assessment results, ICON-Etch was applied three times in total, and treatment procedures were completed in the first appointment, similar to Case 1. One week after the ICON® application, the caries in the interproximal surfaces of teeth 11 and 21 were carefully removed with high speed handpiece, and the teeth were restored using the same materials as in Case 1 (Figure 2).

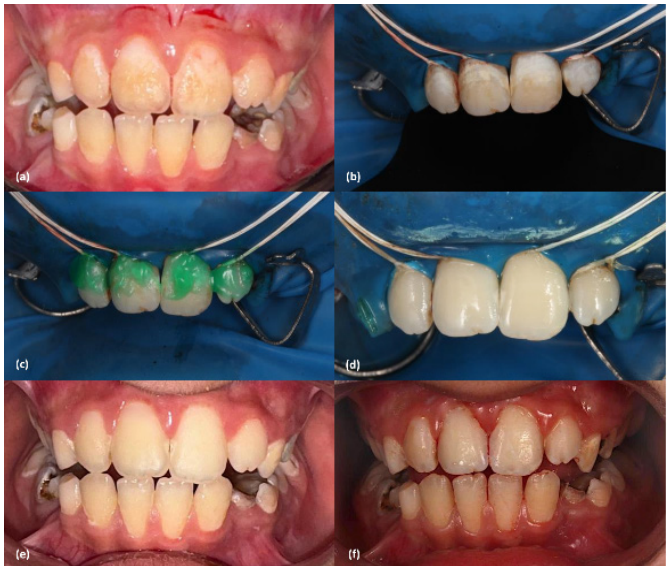

Figure 2. Treatment pictures of Case 2. (a) Initial intra-oral view, (b) Intra-oral view after rubber dam placement, (c) ICON-Etch application, (d) Appearance after ICON-Infiltrant application, (e) Intra-oral view after rubber dam removal, (d) Intra-oral view after removal of carious tissue and composite placement on the interproximal surfaces of teeth 11 and 21

The fluoride toothpaste using was recommended to both patients to support the remineralization process. In the 3-month follow-ups of both cases, visual comparisons based on end-of-treatment photographs clinically recorded no discoloration, indicating the success of the treatment (Figure 3).

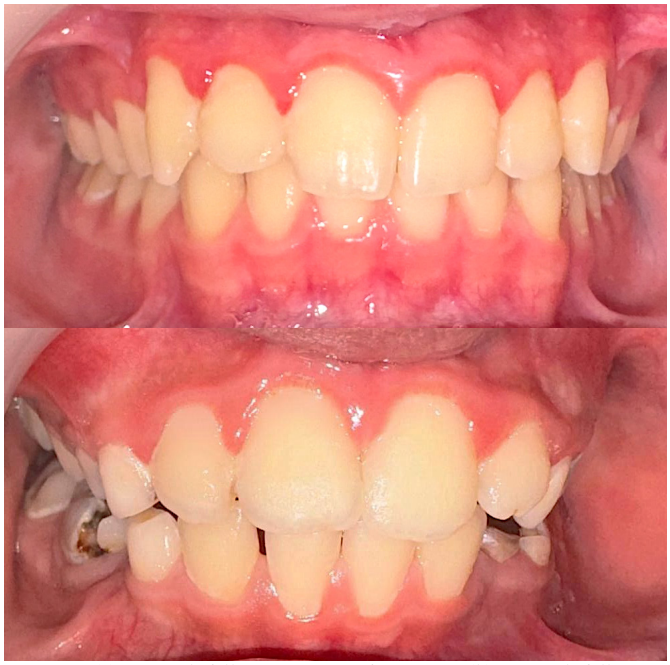

Figure 3. (a) 3-month follow-up picture for Case 1, (b) 3-month follow-up picture for Case 2

DISCUSSION

In the treatment of WSL, known as initial carious lesions, there are numerous different invasive and non-invasive treatment procedures available.[9] In today's context, where the importance of preserving tooth structure has increased, RI technique is a highly successful method that can be employed. For this purpose, ICON®, commercially developed and available in the market, is frequently used, and it constitutes a kit consisting of three syringes with different contents. It includes ICON-Etch containing 15% HCl, ICON-Dry containing ethanol, and ICON-Infiltrant containing TEGDMA.[1] ICON-Etch exhibits a caryostatic effect on bacteria present in the lesion, while ICON-Infiltrant facilitates better penetration into the lesion. ICON-Dry is used to remove excess water from the lesion and to allow for a more accurate visual assessment. ICON-Infiltrant fills the porous structure of the lesion, preventing bacterial growth and ensuring that the refractive index of the lesion is close to that of enamel.[5] These case reports aim to describe the treatment of WSLs with caries cavities, with minimal tissue removal from the tooth structure, using combinated different treatment methods.

Simon and colleagues[10] evaluated the effectiveness of RI and CPP-ACP application in the treatment of post-orthodontic WSLs. They noted that both methods could achieve permanent and desired aesthetic improvement, suggesting that the use of both could be recommended. Torres et al.[11] in 2011 reported that RI technique was more effective than fluoride application in the treatment of WSLs. In this case report, considering the high aesthetic expectations of the patients, the treatment duration, and cooperation, the RI technique has been preferred.

Omota and colleagues[1] stated that the RI technique is an effective and successful MI method in stopping the progression of caries in the patient's anterior teeth in their case report. Cazzolla et al.[8] used the RI technique in the treatment of cavity-free WSLs observed after orthodontic treatment in their case report. They mentioned that, there was no clinically observed recurrence of caries or significant discoloration on the teeth where the application was performed after 4-year long-term follow-up. In Sadıkoğlu's[9] case report, combined approach of RI technique and composite restoration was applied in the treatment of teeth with both WSLs and cavitated caries. It was mentioned that the visibility of white opaque lesions disappeared, composite could be applied without the need for invasive removal of tooth structure, and there were no issues reported during the 1-year long-term follow-up.[9] In contrast to this case report, in the case 2, the use of a high-speed handpiece was required to remove carious tissues on the interproximal surfaces. However, it is considered that the RI application still reduced the amount of tissue that would need to be removed compared to if it had not been applied. The shorter follow-up duration in this study is another limitation.

Torres et al.,[12] treated a tooth with molar incisor hypomineralization using a combination of macroabrasion, RI technique, and composite restoration, stated that after applying ICON-Infiltrant in the same session, composite restoration could be performed without the need for reapplication of an adhesive agent. In these case reports, since the restoration material could not be applied on the same day in both cases, it was deemed necessary to perform etching and subsequent adhesive agent application on the restored teeth. However, there is a need for studies comparing the long-term outcomes, including discoloration and bond strength, of restorative procedures performed with or without the application of adhesive agent at the same day.

CONCLUSION

The RI technique is minimally invasive and non-traumatic method that can be used in the treatment of WSLs, proving to be highly effective and successful in remineralizing the lesion and filling sub-surface porosities. Additionally, the advantage of having a treatment duration of no more than a few sessions is significant compared to other treatment options.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Reviewer Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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