KAFKAS TIP BİLİMLERİ DERGİSİ

Kafkas Journal of Medical Sciences

ISSN: 2146-2631
eISSN: 2587-053X

Cilt / Volume **14**
Sayı / Issue **1**
Nisan / April **2024**

ISSN: 2146-2631
eISSN: 2587-053X

KAFKAS
TIP BİLİMLERİ DERGİSİ

Kafkas Journal of Medical Sciences

Kafkas J Med Sci

Bu dergi Kafkas Üniversitesi Tıp Fakültesi'nin akademik yayın organıdır.
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36300 KARS - TÜRKİYE
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Fax: 474 225 11 93
E-mail: meddergi@kafkas.edu.tr
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Yayın Hizmetleri *(Publication Service)*

Tasarım ve Uygulama *(Graphic Design)*
BAYT Bilimsel Araştırmalar Basın Yayın ve Tanıtım Ltd. Şti.
Ziya Gökalp Cad. 30/31, Kızılay - Ankara
Tel: (312) 431 30 62
www.bayt.com.tr

Baskı *(Printing)*
Miki Matbaacılık Ltd. Şti.
Matbaacılar Sitesi, 560 Sk. No:27, İvedik - Ankara
Tel: (312) 395 21 28

Baskı Tarihi *(Printing Date)*: **30 Nisan 2024**

Danışma Kurulu *(Advisory Board)*

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İçindekiler / *Contents*

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

OLGU SUNUMU / *CASE REPORT*

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Short-Term Effect of Prostaglandin Group Antiglaucomatous Drugs on Choroid Thickness

Prostaglandin Grubu Antiglokomatöz İlaçların Koroid Kalınlığı Üzerine Kısa Dönem Etkisi

Muslum Toptan[1], Ali Simsek[1]

[1]*Opthalmology Department, Harran University Medical Faculty, Sanliurfa, Türkiye*

ABSTRACT

Aim: *To evaluate the effects of patients with whom we started prostaglandin analogues for primary open-angle glaucoma (POAG) by measuring the choroidal thickness with Enhanced-Depth Imaging - Optical Coherence Tomography (EDI-OCT).*

Material and Method: *Thirty-two eyes of 32 patients (Group 1) in whom prostaglandin analogues antiglaucomatous drops were initiated, 32 eyes of 32 patients (Group 2) who were initiated with different groups of antiglaucomatous drugs, and 32 eyes of 32 healthy individuals (control group) were included in the study. Before the drug, these groups' submacular choroidal thickness (CT) and intraocular pressure (IOP) were measured with EDI-OCT. Submacular CT of the same groups was measured in the 1st week, the 1st month, and the 3rd month after starting the drug..*

Results: *A significant increase was detected in mean submacular CT thickness measurements with drug use in both Group 1 and Group 2 (p<0.001). Although the choroidal thickness was thinner in pre-treatment glaucoma groups, there was no significant difference in CT (p=0.072). There was no statistically significant difference between the mean Submacular CT groups of all groups at three months (p=0.198). The decrease in IOP in the glaucoma groups was statistically significant (p<0.001, p<0.001, respectively).*

Conclusion: *A significant increase in submacular CT values was detected in patients who started prostaglandin or non-prostaglandin antiglaucomatous due to POAG. In addition, no statistically significant difference was found between the glaucoma groups regarding choroidal change.*

Key words: *choroidal thickness; optical coherence tomography; prostaglandin analogues; intraocular pressure*

ÖZET

Amaç: *Primer açık açılı glokom (PAAG) nedeni ile prostaglandin analogu başladığımız hastaların koroid kalınlığını Enhanced-Depth Imaging - Optical Coherence Tomography (EDI-OCT) ile ölçerek etkilerini değerlendirmek.*

Materyal ve Metot: *Prostaglandin analogu antiglokomatöz damla başlanan 32 hastanın 32 gözü (Grup 1), farklı grup antiglokomatöz ilaç başlanan 32 hastanın 32 gözü (Grup 2), 32 sağlıklı bireyin 32 gözü (kontrol grubu) çalışmaya dâhil edildi. İlaç öncesi bu grupların EDI-OCT ile submaküler koroid kalınlığı (KK) ve göz içi basıncı (GİB) ölçüldü. İlaç başlandıktan sonra 1. hafta, 1. ay ve 3. ayda submaküler KK'ları incelendi.*

Bulgular: *Hem Grup 1 hem de Grup 2'de ilaç kullanımı ile ortalama submaküler KK ölçümlerinde anlamlı artış saptandı (p<0,001). Tedavi öncesi glokom gruplarında koroid kalınlığı daha ince olmasına rağmen gruplar arasında KK'da anlamlı fark yoktu (p=0,072). Submaküler KK ölçümlerinde 3. ayda gruplar arasında istatiksel olarak anlamlı fark tespit edilmedi (p=0,198). Glokom gruplarında GİB'deki düşüş istatistiksel olarak anlamlı bulundu (sırasıyla p<0,001, p<0,001).*

Sonuç: *PAAG nedeniyle prostaglandin veya prostaglandin dışı antiglokomatöz başlanan hastalarda submaküler KK değerlerinde anlamlı artış saptandı. Ayrıca koroid değişikliği açısından glokom grupları arasında istatistiksel olarak anlamlı fark bulunmadı.*

Anahtar kelimeler: *koroid kalınlığı; optik kohorens tomografi; prostoglandin analogları; göz içi basıncı*

Introduction

Glaucoma is a chronic progressive optic neuropathy resulting in permanent loss of vision[1]. Medical treatment in which prostaglandins play an important role is generally effective. Prostaglandin analogues are a frequently employed drug group in glaucoma due to their efficacy in monotherapy, ease of use in a single dose, and lack of impact on quality of life[2]. Several studies have proved the effectiveness of medications from this group in lowering intraocular pressure (IOP), the most critical risk factor in glaucoma[3]. Prostaglandin analogues reduce IOP by increasing the outflow of aqueous humor via the uveoscleral route and the trabecular meshwork[1,4].

İletişim/Contact: *Muslum Toptan, Medical Faculty, Opthalmology Department, Sanliurfa, Türkiye* • ***Tel:*** *0507 811 15 09* • ***E-mail:*** *muslum.toptan@hotmail.com* • ***Geliş/Received:*** *29.06.2022* • ***Kabul/Accepted:*** *17.01.2024*

ORCID: *Müslüm Toptan: 0000-0002-9795-8228* • *Ali Şimşek: 0000-0002-5077-8721*

Several studies have shown that these prostaglandin analogues used in the treatment of glaucoma increase ocular perfusion pressure and blood flow, which is reported to be positively correlated with the choroidal thickness (CT)[5]. However, some studies have suggested that this increase is associated with a decrease in IOP[6]. In addition, the regulatory capacity of changes in ocular perfusion pressure in the human choroid has recently been shown to be capable of alteration in line with changes in arterial blood pressure and IOP[7]. Prostaglandin group medications have a known potential pro-inflammatory effect and have been linked to ocular inflammation in some cases[8]. There have also been case reports of prostaglandin analogues causing choroidal detachment[9].

The fact that optic neuropathy also develops in the case of normal IOP suggests that factors other than IOP elevation may be involved in the pathogenesis of glaucoma. Enhanced-depth imaging (EDI) is a new optical coherence tomography (OCT) technique permitting detailed evaluation of the choroid layer. Evaluating CT in glaucomatous eyes using this new method will also contribute to a greater understanding of the relationship between glaucoma and the choroid and the effect on the choroid of the drugs used in medical treatment. A limited number of studies have examined changes in the choroid coat developing with anti-glaucomatous treatment, and we think that studies in this area will contribute to a better understanding of the effect of topical anti-glaucomatous medications on the choroid.

The present study aimed to investigate CT using EDI-OCT in patients started on prostaglandin analogues due to primary open-angle glaucoma (POAG).

Materials and Methods

This prospective study was conducted with patients who presented to the Harran University Faculty of Medicine Eye Clinic Glaucoma Unit between September 2018 and March 2021. The research commenced following receipt of permission from the Harran University Medical Surgery and Drug Research Ethics Committee. Thirty-two eyes of 32 patients aged 50–70 were diagnosed with POAG. They started on prostaglandin analog anti-glaucoma drops (Group 1), 32 eyes of 32 patients started on different anti-glaucomatous group medications (Group 2), and 32 eyes of 32 healthy individuals from a similar age group but without glaucoma representing the control group were included in the study.

Patients with visual acuity of 0.2 or worse, retinal sensitivity affected by environmental turbidity, and any condition capable of affecting retinal sensitivity or the visual field (such as cataract, corneal turbidity, vitreous turbidity, or age-related macular degeneration), diabetes mellitus, systemic diseases affecting retinal sensitivity such as uveitis or Behçet's disease, a previous history of ocular surgery, refractive error exceeding ±1.0 diopters (D), or patients with problematic choroidal-scleral differentiation at OCT were excluded from the study.

Patients in the first group were started on one of the prostaglandin analogues latanoprost (Xalatan®), travoprost (Travatan®), or bimatoprost (Lumigan®). In contrast, those in Group 2 were started on one of the carbonic anhydrase inhibitors, beta-blockers, or alpha-adrenergic agonists. The individuals in the third group had no ocular disease. The patients were not using any medication other than the anti-glaucomatous agents. Corrected near and far visual acuity, anterior segment, and fundus examination, angle examination using a Goldmann three-mirror contact lens, IOP measurement using a Goldmann applanation tonometer, axial length measurement using an ultrasonic biometer (NIDEK US-4000 Echoscan Gamagori, Japan), topographic pachymetry using a Pentacam, and central corneal thicknesses measurements were performed at the first examination and follow-ups at the first week and the first and third months. Perimetric tests (central 30–2 threshold test with the SITA-Fast strategy) were conducted using a Humphrey Field Analyzer (Humphrey Field Analyzer-750; Carl Zeiss Meditec, Dublin, CA, USA), and mean deviation (MD) and pattern standard deviation (PSD) values were recorded. The POAG group consisted of patients with IOP exceeding 21 mmHg without medication, with an open and normal anterior segment angle at gonioscopic examination, with glaucoma-specific optic nerve head damage and visual field defect. In addition, all patients' submacular CT was measured using spectral domain OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany), and enhanced-depth imaging (EDI) mode was used for CT. A single technician performed imaging without knowledge of the research, and thickness measurements were carried out by a single evaluator blinded to the study groups. The first measurement point on the macular cross-section at OCT was beneath the fovea, and subsequent measurements were taken in the nasal and temporal directions. This measurement was based on the distance between the posterior edge of the retinal pigment epithelium

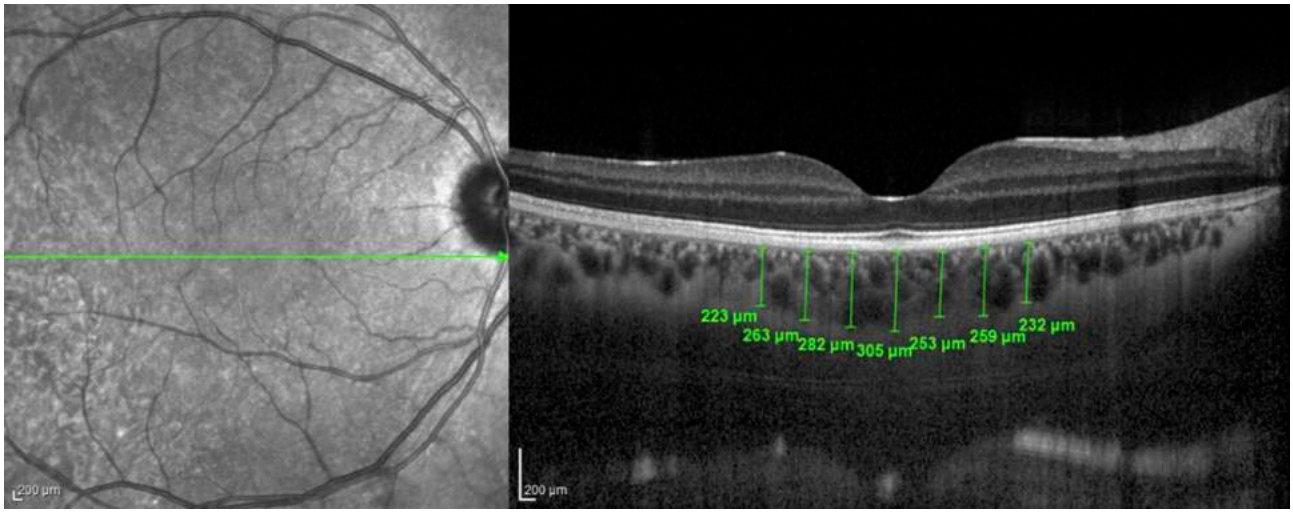

Figure 1. *Seven choroidal thickness measurements from the macular region.*

Table 1. *Demographic and clinical characteristics of the participants in the study groups*

	Group 1	Group 2	Control	p
Age (years)	58.60±6.54	58.80±5.34	57.66±5.65	0.850
Sex(F/M)	14/18	15/17	16/16	0.915
Perimetric MD (dB)	-8.47±1.38	-8.44±1.40	-0.54±0.30	**<0.001**
Perimetric PSD (dB)	8.47±1.19	8.51±1.28	1.81±0.41	**<0.001**
Corneal thickness (µm)	524.83±5.34	525.56±5.97	524.73±3.36	0.782
Axial length (mm)	22.69±0.94	22.86±0.96	22.84±0.96	0.962

MD: Mean deviation; **PSD:** Pattern standard deviation

(RPE) and the choroid sclera junction. The user manually measured the vertical distance between these two points in microns with the assistance of the device's ruler function. This first measurement was recorded with the abbreviation SF (subfoveal). Six further measurement points, three nasal and three temporal, were then established at 500-micron intervals, with the first measurement point being fixed. These points in the nasal region were referred to as N1, N2, and N3 from the center toward the periphery, and those in the temporal regions were referred to as T1, T2, and T3 from the center toward the periphery (Fig. 1).

Statistical Analysis

The data obtained were analyzed using IBM Statistical Package for Social Sciences (SPSS) program version 23.0 (IBM Inc., Chicago, IL, USA) software. When parametric conditions were met, the Mann-Whitney U-test was used to compare measurement data between the two glaucoma groups. Analysis of variance (ANOVA) was applied to compare measurement data among the three groups when parametric conditions were established and the Kruskal-Wallis test if parametric conditions were not met. Repeated measures ANOVA was applied for consecutive measurements, while descriptive data were compared using the chi-square test. Measurement data were expressed as mean ± standard deviation and descriptive data as numbers and percentages. p values <0.05 were regarded as statistically significant.

Results

No significant difference was determined among the three groups regarding age, sex, axial length, or corneal thickness (p>0.05 for all). The demographic characteristics and clinical findings of all three groups are shown in Table 1. Mean deviation values in groups 1 and 2, the glaucoma groups, differed significantly from those in the control group p<0.001 for both).

There was no significant difference between the glaucoma groups regarding MD, PSD, IOP, or corneal thickness values (p=0.871, p=0.863, p=0.964, and p=0.782, respectively).

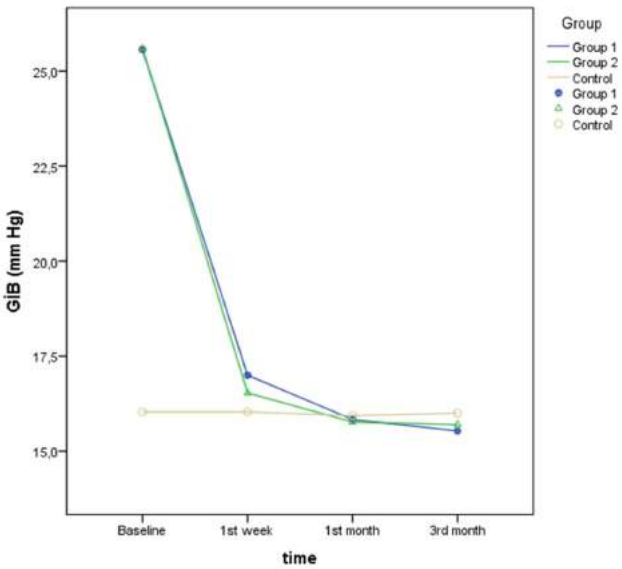

Figure 2. *Changes in IOP values in the study groups.*

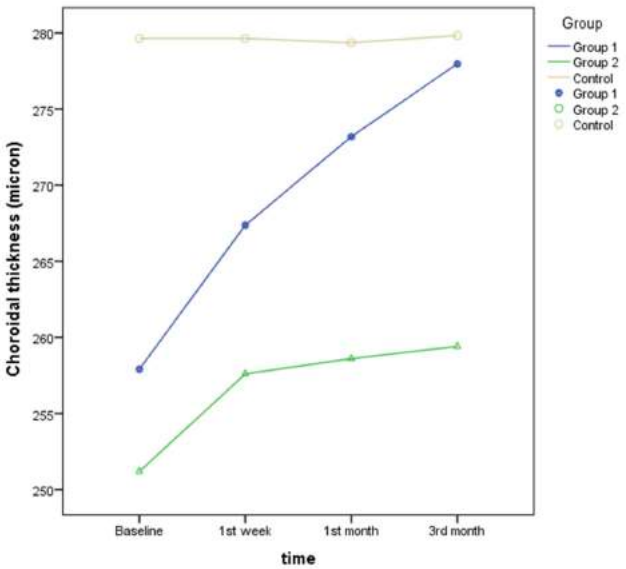

Figure 3. *Changes in mean choroidal thickness values in the study groups.*

Table 2. *Distribution of eyes. IOP and submacular choroidal thickness in the groups*

		Baseline	1st week	1st month	3rd month	p
Group 1	IOP (mm Hg)	25.5±1.6	17.0±1.3	15.8±1.2	15.5±1.2	**<0.001**
	CT (µm)	257.9±53.3	267.3±52.0	273.1±52.0	277.9±52.0	**<0.001**
Group 2	IOP (mm Hg)	25.6±1.8	16.5±0.9	15.7±1.5	15.7±1.2	**<0.001**
	CT (µm)	251.1±44.1	257.6±44.6	259.4±42.9	259.4±42.9	**<0.001**
Control	IOP (mm Hg)	16.0±2.6	16.0±2.4	15.9±2.1	16.0±2.4	0.964
	CT (µm)	279.6±47.7	279.6±47.7	279.3±47.2	279.8±47.4	0.268

IOP: Intraocular pressure; **CT:** Choroidal thickness (µm).

Twelve cases in the prostaglandin group were started on latanoprost, ten on travoprost, and ten on bimatoprost. Mean CT and IOP values by groups at baseline, one week, and one and three months are shown in Table 2.

Comparison of baseline IOP levels with those at one week and one and three months revealed significant decreases in both Group 1 and Group 2. In contrast, a substantial increase was determined in CT values ($p<0.001$). Changes in IOP and mean CT at consecutive measurements in all three study groups are shown in Figures 2 and 3.

Although there was no statistically significant difference in pre-treatment CT between the two glaucoma groups (Groups 1 and 2) and the control group, CT was lower in the glaucoma groups ($p=0.072$). In the third month, the mean CT in the control group was 279.8±47.4 µm, compared to 277.9±52.0 µm in Group 1 and 259.4±42.9 µmin Group 2. Mean CT values at submacular measurements in the third month were highest in the control group, followed by Group 1 and Group 2. However, there was no statistically significant difference among the three groups ($p=0.198$).

No statistically significant difference was observed between the glaucoma groups regarding changes in IOP or CT ($p=0.715$ and $p=0.341$, respectively). Changes in submacular CT at the seven measurement points at the end of the third month compared to baseline values are shown in Table 3.

The subfoveal measurements were the highest mean values among the seven measurements taken from the macular region. At the same time, CT on the temporal side was greater than on the nasal side. CT other than SF at all times points in groups 1 and 2 and the control group, from highest to lowest, were at T1, N1, T2, N2, T3, and N3. Statistical analysis showed that CT increased significantly in groups 1 and 2 at all seven points. At the same time, no significant difference was found in the control group.

Table 3. *Changes in choroidal thickness at the seven submacular measurement points*

	Group 1			Group 2			Control		
	Baseline CT (µm)	3rd month CT (µm)	p	Baseline CT (µm)	3rd month (µm)	p	Baseline CT (µm)	3rd month CT (µm)	P
T3	240.9±53.8	264.4±53.1	<0.001	233.9±42.8	241.7±43.2	<0.001	264.1±47.5	264.3±47.4	0.165
T2	258.3±54.0	279.5±52.3	<0.001	246.7±45.4	256.0±44.5	<0.001	281.5±47.3	281.9±47.4	0.167
T1	269.5±52.3	291.9±51.1	<0.001	269.8±45.4	278.0±43.8	<0.001	295.5±48.1	296.0±48.1	0.164
SF	296.5±52.3	317.1±50.7	<0.001	295.3±46.1	305.0±43.9	<0.001	322.4±50.9	322.9±50.1	0.326
N1	269.6±54.7	291.3±53.8	<0.001	263.1±50.7	271.8±48.7	<0.001	283.2±52.9	282.8±52.3	0.502
N2	248.2±59.8	266.8±58.5	<0.001	241.6±53.3	248.8±52.9	<0.001	268.3±54.4	268.7±54.4	0.163
N3	222.0±59.8	234.6±56.4	<0.001	207.7±50.8	214.2±50.6	<0.001	242.2±55.5	241.9±54.4	0.502

CT: Choroidal thickness (µm).

Discussion

The choroid is a highly vascularized structure with considerable blood flow. The thickness may change in line with variations in IOP[10]. Although there have been various studies of the relationship between glaucomatous optic neuropathy and impaired choroidal circulation or optic nerve head blood flow, the role of the choroid in glaucomatous optic neuropathy is still unclear[11].

Recent advances in the imaging of the ocular posterior segment, particularly the entry into EDI OCT, have permitted a more detailed examination of the choroid layer and have again raised the question of the relationship between glaucoma and CT. The present study aimed to assess the effect of prostaglandin-group anti-glaucoma drug use on submacular CT.

Mwanza et al. reported no significant differences in CT measurements taken from the macula region using EDI OCT in cases with glaucoma and normal individuals[12]. Maul et al. also reported no significant difference in a similar study[13]. Song et al. reported a thinner submacular choroid in patients with glaucoma, although the difference was not statistically significant[14]. In the present study, while there was no significant difference in pre-treatment CT between the glaucoma groups (groups 1 and 2) and the control group, the choroid was thinner in the glaucoma groups.

Any topical glaucoma medication will alter ocular perfusion pressure due to its ocular hypotensive effect. The ocular perfusion pressure of the human choroid has been shown to vary in association with arterial blood pressure or IOP[7,15]. Since choroidal venous pressure and IOP are closely interrelated, any decrease in IOP will lead directly to an increase in ocular perfusion[16]. Latanoprost has been found to positively affect ocular perfusion pressure, ocular blood flow, and choroidal blood flow[5,6]. Most studies have shown that blood flow increases significantly following treatment, including latanoprost. Based on the findings of studies involving B-receptor antagonists and carbonic anhydrase inhibitors, the vasomotor effect contributes directly to changes in ocular perfusion pressure[17]. Intraocular pressure levels play a crucial role in changes in CT. Moreover, any decrease in IOP is thought to have an improving effect on ocular blood flow regulation[18].

Çalişkan et al. examined CT and axial length changes following mannitol infusion in patients with high IOP. They reported that a decrease in IOP following infusion in such patients caused an increase in CT values[19]. Similarly, Akahori et al. observed that the more significant the decrease in IOP, the more remarkable the increase in CT[20]. The change in CT after treatment in our glaucoma groups may, therefore, be related to a decrease in IOP. In addition, no significant difference was observed in IOP changes between Group 1 and Group 2. The greater increase in CT in the cases using prostaglandin, even though both glaucoma treatments produced a decrease in IOP, may derive from the different effect mechanisms of the two medications.

In contrast to other anti-glaucoma agents, prostaglandins increase the outflow of aqueous humor via the uveoscleral route. Aqueous humor passes from there to the suprachoroidal space via the vortex veins that drain the choroid and thus enter the circulation. Prostaglandins can, therefore, raise CT more than non-prostaglandin anti-glaucoma medications. In addition, a slight increase in CT in the non-prostaglandin anti-glaucoma medication group may also occur as a result of a decrease in IOP[21].

Kola et al. reported a significantly greater CT in cases of ankylosing spondylitis, an inflammatory disease than in a healthy control group. Those authors suggested that this difference might be due to the inflammatory effect of prostaglandins[22]. Boyraz et al. observed

a significant increase in foveal thickness and foveal volume in patients using prostaglandin for three years or longer. They suggested that since prostaglandins exert an inflammation-triggering effect, they may also increase foveal and macular thickness by exacerbating subclinical inflammation[23]. The increased CT observed in patients receiving prostaglandin analog therapy may be due to these inflammation-triggering effects.

Glaucoma is a focal disease that usually affects the inferotemporal or superotemporal nerve fiber layers. Due to its focal nature, there is a strong likelihood of a link between the choroidal layer and the area around the optic disk, known as the peripapillary zone. Nakakura et al. observed no significant difference between normal individuals and those with glaucoma in their comparison of macular CT in cases of POAG[24]. Similarly, both Hirata et al. and Mawanza et al.'s studies reported greater thicknesses in the temporal part of the macula than in the nasal part[25,12]. The present study supports the idea that the macula's temporal region is thicker than the nasal region in cases of POAG. The highest of the seven measurements in the macular region in the present study were those from the subfoveal region. When the six measurements other than SF were compared at all time points, the mean CT values were highest to lowest in groups 1 and 2, and the control group was in T1, N1, T2, N2, T3, and N3. Statistical analysis revealed a significant increase in CT in the seven measurement points in Group 1 and Group 2 but no significant difference in the control group.

Akyol et al. investigated the effects on CT of bimatoprost against those of a brinzolamide/timolol maleate fixed combination. They observed a statistically significant difference between the two groups, the increase in thickness being greater in the bimatoprost group[26]. No significant difference was observed in the present study between prostaglandin and non-prostaglandin anti-glaucoma therapy, although consistent with that study, the increase in CT was greater in patients using prostaglandin.

Aksoy et al. confirmed that CT is affected by several factors. For example, they observed 30–60 μm changes in diurnal CT and that intravenous acetazolamide use led to increased CT[27]. We therefore measured CT values within a limited time frame (09:00–12:00 hours), and patients using oral carbonic anhydrase inhibitor (acetazolamide) were excluded. In addition, systolic blood pressure values and hypercholesterolemia are also known to affect CT[28]. However, these parameters were not investigated in this study. Other limitations of this study are the low case number, the short follow-up period, and the fact that CT was measured manually.

In conclusion, examination of submacular CT in patients started on prostaglandin or non-prostaglandin anti-glaucoma therapies due to POAG in this study revealed a significant increase in both groups. No significant difference was determined between the glaucoma groups and the control group at the end of three months. No significant difference was found between the glaucoma groups regarding IOP or choroidal changes. Our study supports the idea that anti-glaucoma medications increase submacular CT. Further, more extensive studies are now needed to determine the role of choroidal circulation in the pathogenesis of glaucoma.

Funding

No financial support was given to the present study.

Data Availability

All data are available; please contact the corresponding author.

Compliance with Ethical Standards

Conflict of Interest

The authors declare no conflict of interest.

Ethical Approval

All procedures performed in studies involving human participants were under the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Harran University Institutional Evaluation Committee and Ethical Committee (Protocol Number 10/08/2018-E. 31565).

Informed consent

Informed consent was obtained from all participants in the study.

Consent for publication

It was obtained from all individual participants included in the study.

References

1. Ho H, Daas A, Ho J, Alaghband P, Galvis EA, de Antonio Ramirez A, et al. Intraocular pressure changes following topical ocular hypotensive medications washout. Br J Ophthalmol. 2021;105:205–9.
2. Li F, Huang W, Zhang X. Efficacy and safety of different regimens for primary open-angle glaucoma or ocular hypertension: a systematic review and network meta-analysis. Acta Ophthalmol. 2018;96(3):e277–e284.
3. Yildirim N, Sahin A, Gultekin S. The effect of latanoprost, bimatoprost, and travoprost on circadian variation of intraocular pressure in patients with open-angle glaucoma. J Glaucoma. 2008;17:36–9.
4. Toris CB, Gabelt BT, Kaufman PL. Update on the mechanism of action of topical prostaglandins for intraocular pressure reduction. Surv Ophthalmol. 2008;53:107–20.
5. Stjernschantz J, Selén G, Astin M, Resul B. Microvascular effects of selective prostaglandin analogues in the eye with special reference to latanoprost and glaucoma treatment. Prog Retin Eye Res. 2000;19:459–96.
6. Harris A, Garzozi HJ, McCranor L, Rechtman E, Yung CW, Siesky B. The effect of latanoprost on ocular blood flow. Int Ophthalmol. 2009;29:19–26.
7. Polska E, Simader C, Weigert G, Doelemeyer A, Kolodjaschna J, Scharmann O, et al. Regulation of choroidal blood flow during combined changes in intraocular pressure and arterial blood pressure. Invest Ophthalmol Vis Sci. 2007;48:3768–74.
8. Lee D, Mantravadi AV, Myers JS. Patient considerations in ocular hypertension: role of bimatoprost ophthalmic solution. Clin Ophthalmol. 2017;11:1273–80.
9. Cheggour M, Gambrelle J. [Massive choroidal detachment secondary to topical use of bimatoprost: Report of two cases]. J Fr Ophtalmol. 2012;35:176–80.
10. Park Y, Kim HK, Cho KJ. Comparison of peripapillary and macular choroidal thickness and ganglion cell complex thickness in glaucomatous and healthy eyes. Int J Ophthalmol. 2019;12:603–6.
11. Zhang Z, Yu M, Wang F, Dai Y, Wu Z. Choroidal Thickness and Open-Angle Glaucoma: A Meta-Analysis and Systematic Review. J Glaucoma. 2016;25:e446–54.
12. Mwanza JC, Hochberg JT, Banitt MR, Feuer WJ, Budenz DL. Lack of association between glaucoma and macular choroidal thickness measured with enhanced depth-imaging optical coherence tomography. Invest Ophthalmol Vis Sci. 2011;52:3430–5.
13. Maul EA, Friedman DS, Chang DS, Boland MV, Ramulu PY, Jampel HD, et al. Choroidal thickness measured by spectral domain optical coherence tomography: factors affecting thickness in glaucoma patients. Ophthalmology. 2011;118:1571–9.
14. Song YJ, Kim YK, Jeoung JW, Park KH. Assessment of Open-Angle Glaucoma Peripapillary and Macular Choroidal Thickness Using Swept-Source Optical Coherence Tomography (SS-OCT). PLoS One. 2016;11(6):e0157333.
15. Vetrugno M, Cardascia N, Cantatore F, Sborgia C. Comparison of the effects of bimatoprost and timolol on intraocular pressure and pulsatile ocular blood flow in patients with primary open-angle glaucoma: A prospective, open-label, randomized, two-arm, parallel-group study. Curr Ther Res Clin Exp. 2004;65:444–54.
16. Reitsamer HA, Kiel JW. A rabbit model to study orbital venous pressure, intraocular pressure, and ocular hemodynamics simultaneously. Invest Ophthalmol Vis Sci. 2002;43:3728–34.
17. Fuchsjager-Mayrl G, Georgopoulos M, Hommer A. Effect of dorzolamide and timolol on ocular pressure: blood flow relationship in patients with primary open-angle glaucoma and ocular hypertension. Invest Ophthalmol Vis Sci. 2010;51:1289–96.
18. Martinez A, Sanchez-Salorio M. Predictors for visual field progression and the effects of treatment with dorzolamide 2% or brinzolamide 1% each added to timolol 0. 5% in primary open-angle glaucoma. Acta Ophthalmol. 2010;88:541–52.
19. Çalişkan S, Uğurbaş SC, Alpay A, Uğurbaş SH. Changes in the Choroidal Thickness and Axial Length Upon Mannitol Infusion in Patients With Asymmetric Intraocular Pressure. J Glaucoma. 2016;25:891–5.
20. Akahori T, Iwase T, Yamamoto K, Ra E, Terasaki H. Changes in Choroidal Blood Flow and Morphology in Response to Increase in Intraocular Pressure. Invest Ophthalmol Vis Sci. 2017;58:5076–85.
21. Caprioli J, Coleman AL. Blood Flow in Glaucoma Discussion. Blood pressure, perfusion pressure, and glaucoma. Am J Ophthalmol. 2010;149:704–12.
22. Kola M, Kalkisim A, Karkucak M, Turk A, Capkin E, Can I, et al. Evaluation of choroidal thickness in ankylosing spondylitis using optical coherence tomography. Ocul Immunol Inflamm. 2014;22:434–8.
23. Boyraz S, Aritürk N. The Effect on Macular Thickness of Prostaglandin Group Eye Drops for Glaucoma. Glo-Kat. 2010;5:75–8.
24. Nakakura S, Yamamoto M, Terao E, et al. The whole macular choroidal thickness in subjects with primary open angle glaucoma. PLoS One 2014;9(10):e110265. Nakakura S, Yamamoto M, Terao E, Nagasawa T, Tabuchi H, Kiuchi Y. The whole macular choroidal thickness in subjects with primary open angle glaucoma. PLoS One. 2014;9:e110265.
25. Hirata M, Tsujikawa A, Matsumoto A, Hangai M, Ooto S, Yamashiro K, et al. Macular choroidal thickness and volume in normal subjects measured by swept-source optical coherence tomography. Invest Ophthalmol Vis Sci. 2011;52:4971–8.
26. Akyol N, Kalkisim A, Turk A, Kola M, Imamoglu HI. Evaluation of the effects on choroidal thickness of bimatoprost 0. 03% versus a brinzolamide 1. 0%/timolol maleate 0. 5% fixed combination. Cutan Ocul Toxicol. 2017;36:397–403.
27. Aksoy Y, Çolakoglu K, Kar T, Sevinc MK, Eyi YE. Choroidal thickness is affected by more factors than estimated. Invest Ophthalmol Vis Sci. 2014;55:1311.
28. Usui S, Ikuno Y, Akiba M, Maruko I, Sekiryu T, Nishida K, et al. Circadian changes in subfoveal choroidal thickness and the relationship with circulatory factors in healthy subjects. Invest Ophthalmol Vis Sci. 2012;53:2300–7.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Determination of Osteopenic and Osteoporotic Spine with Hounsfield Unit in Spinal Fusion Surgery

Spinal Füzyon Cerrahisinde Hounsfield Unit ile Osteopenik ve Osteoporotik Omurganın Belirlenmesi

Guray Bulut[1], M. Ozgur Taskapilioglu[2]

[1]Department of Neurosurgery, Medipol University School of Medicine, Istanbul; [2]Department of Neurosurgery, Bursa Uludag University School of Medicine Bursa, Türkiye

ABSTRACT

Aim: *Bone mineral density (BMD) is vital in spinal fusion surgery. Dual X-ray absorptiometry (DEXA) is the gold standard for evaluating BMD. In this study, we aim to assess the bone density of the patients using Hounsfield units (HU) who underwent spinal surgery with instrumentation.*

Material and Method: *Computed tomography (CT) and DEXA results of 99 cases of 40 years of age or older who had posterolateral fusion operation between 2014 and 2017 were evaluated retrospectively. The HU values of the vertebral body obtained from the lumbar CT, which is routinely used in surgical planning, were measured with the image archiving and communication system (PACS; Maroview, Infinitt Healthcare). Three measurements were taken from each vertebra. Hounsfield unit values were determined according to age groups. These results were compared with the L1–4 DEXA results acquired before the operation and/ or within six months.*

Results: *HU values of patients obtained from CT were classified between four age groups. Hounsfield unit values of each vertebral level were compared with the T score obtained with DEXA. The correlations of the HU value with the T score were significant (p <0.001). The mean HU values of the compared levels decreased consistently over the ten years. The differences were statistically significant. There was no significant difference between HU values in age groups.*

Conclusion: *Estimating the osteopenic/ osteoporotic spine by measuring the HU values from CT is a simple, cost-effective method that helps surgical planning at instrumentation.*

Key words: *Hounsfield unit; lumbar vertebrae; instrumentation; posterolateral fusion; osteoporosis; spine*

ÖZET

Amaç: *Kemik mineral yoğunluğu (KMY), spinal füzyon cerrahisinde önemli bir faktördür. BMD'yi değerlendirmek için Dual X-ray absorpsiyometri (DEXA) altın standarttır. Bu çalışmada, enstrümantasyon ile spinal cerrahi uygulanan Hounsfield üniteleri (HU) kullanan hastaların kemik yoğunluğunu araştırmayı amaçladık.*

Materyal ve Metot: *2014–2017 yılları arasında posterior transpediküler vida-rod sistemleri ile posterolateral füzyon operasyonu geçiren 40 yaş ve üzeri 99 olgunun BDT ve DEXA sonuçları retrospektif olarak değerlendirildi. Cerrahi planlamada rutin olarak kullanılan lomber BT'den elde edilen vertebra gövdesinin HU değerleri PACS sistemi ile ölçüldü. Her bir omurdan üç ölçüm alındı. Hounsfield ünitesi değerleri yaş gruplarına göre belirlendi. Bu sonuçlar operasyon öncesi ve/veya altı ay içinde alınan L1–4 DEXA sonuçları ile karşılaştırıldı.*

Bulgular: *Bilgisayarlı tomografiden elde edilen hastaların HU değerleri dört yaş grubu arasında sınıflandırıldı. Her bir vertebral seviye için HU değerleri, DEXA ile elde edilen T skoru ile karşılaştırıldı. HU değeri ile T skoru arasındaki korelasyonlar anlamlıydı (p <0,001). Ortalama HU değerleri, dekatlar boyunca karşılaştırılan vertebra seviyelerinde tutarlı bir şekilde azaldı. Farklar istatistiksel olarak anlamlıydı. Yaş gruplarında HU değerleri arasında anlamlı bir fark yoktu.*

Sonuç: *Bilgisayarlı tomografiden HU değerlerini ölçerek osteopenik/osteoporotik omurgayı tahmin etmek, enstrümantasyonda cerrahi planlamaya yardımcı olan basit, uygun maliyetli bir yöntemdir.*

Anahtar kelimeler: *Hounsfield birimi; lomber vertebra; enstrümantasyon; posterolateral füzyon; osteoporoz; omurga*

İletişim/Contact: *M. Ozgur Taskapilioglu, Department of Neurosurgery, Medical School, Uludag University, Bursa, Türkiye* • ***Tel:*** *0224 295 27 40* • ***E-mail:*** *ozgurt@uludag.edu.tr* • ***Geliş/Received:*** *05.08.2022* • ***Kabul/Accepted:*** *09.02.2024*

ORCID: *M. Özgür Taşkapılıoğlu: 0000-0001-5472-9065* • *Güray Bulut: 0000-0002-9318-4800*

Introduction

Success in spinal instrumentation operations is multifactorial. Many factors have an impact on surgical success. The quality of bone is an important prognostic factor for fusion. Severe osteoporosis is an important cause of failure, such as loosening and pulling out of the pedicle screw after spinal fusion surgery[1–4]. Therefore, bone mineral density (BMD) is essential in surgical planning.

Osteoporosis is a systemic disease with increased bone fragility resulting in low bone density and microarchitecture bone tissue degradation. DEXA, used as a routine screening, is the gold standard for BMD measurement. In osteoporotic patients with aortic calcification, severe bone protrusion, sclerosis, and obesity, DEXA results may be normal[1–4].

Measurement of BMD using computed tomography (CT) was an old technique. However, it has not been routinely used. Recent studies have increased the probability of predicting BMD using diagnostic CT images[5–8]. A Hounsfield unit (HU) represents a normalized index of X-ray based on a scale of -1000 defined for air and 0 for water[9]. Hounsfield unit values can be used as a marker for bone mineral density. Lumbar CT is performed routinely to identify anatomical structures before spinal fusion surgery.

In this study, bone density of the spine was evaluated using vertebral HU values obtained from CT scanners routinely used for spinal instrumentation surgery. These results were compared with DEXA results. Standard HU values were tried to be determined to predict normal, osteopenic, and osteoporotic backbone.

Material and Method

This study was approved by the Medipol University Institutional Review Board (05/05/2020–354). Informed consents were obtained from every patient. Ninety-nine patients aged 40 years and older who underwent fusion operation with lumbar spinal instrumentation in our clinic were evaluated retrospectively. Patients with previous lumbar spinal instrumentation, those with secondary diseases that may affect BMD, such as a spinal fracture, spinal tumor, spondylopathy, and systemic disease, and patients under medical treatment for osteoporosis were excluded.

Hounsfield unit values of the vertebral body obtained from lumbar KBT, routinely used in surgical planning, were measured with the PACS system. Patients who had DEXA up to 6 months before the operation or who were considered to be osteopenic and/or osteoporotic in the operation planning were included in the study.

A 126-channel CT scanner (Somatom Perspective, Siemens) was used for CT scans in all patients. An image archiving and communication system (PACS; Maroview, Infinitt Healthcare) was used to calculate the average HU value of the vertebral body. Hounsfield unit measurement for each vertebra was obtained using a protocol described by Schreiber et al.[9]. The HU calculation was measured from L1 to L5 in three locations: inferior to the upper cortex, the middle of the vertebral body, and the top of the lower cortex (Fig. 1). For the

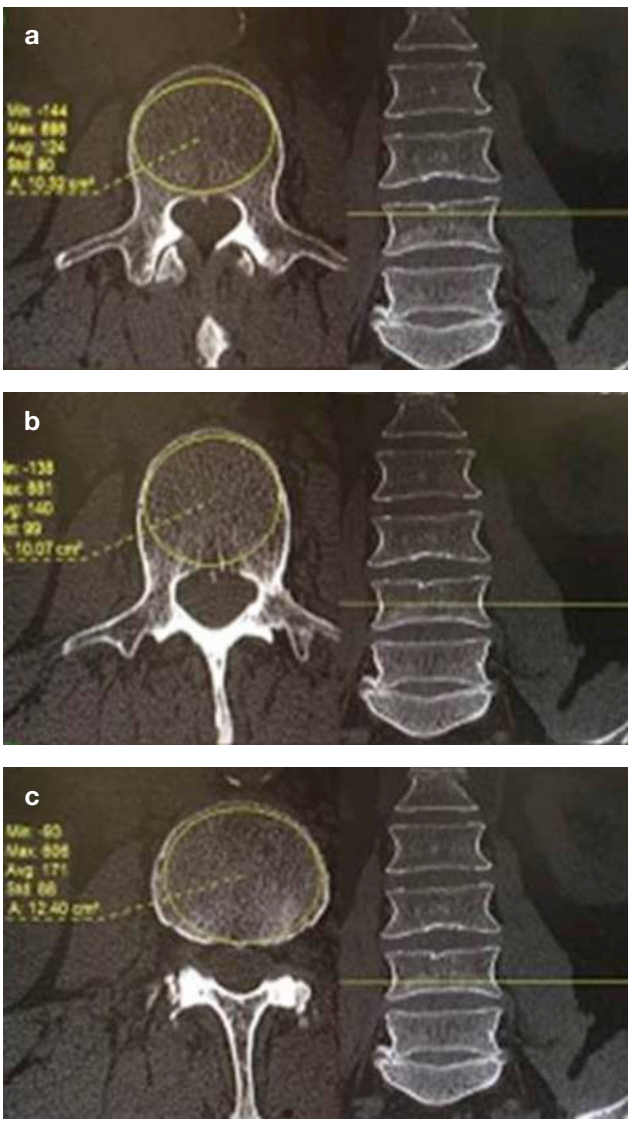

Figure 1 a-c. *Measuring HU with CT: inferior of the upper cortex (a), middle of the vertebral body (b), above the lower cortex (c). When the largest possible elliptical area, excluding cortical edges, is drawn with the PACS system, the system automatically calculates the HU value.*

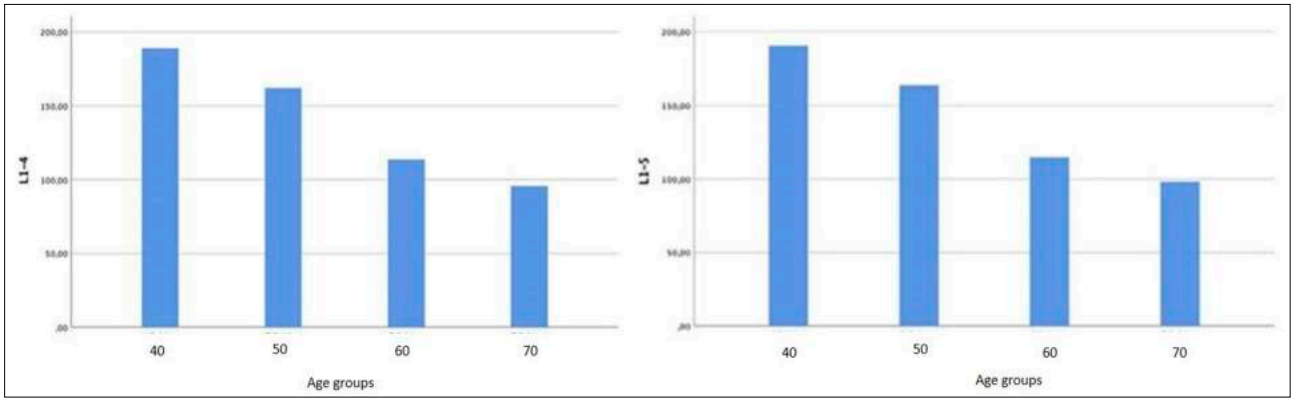

Figure 2. *Decrease of L1–4 and L1–5 HU values in proportion to age.*

averages to be standard for each measurement, the largest possible elliptical area was drawn, except for the cortical edges. By calculating the mathematical average of HU values in three axial slices, a HU value was calculated for each lumbar vertebra. In DEXA scans, results were given according to the L1–4 vertebrae. Hounsfield unit results compared with both L1-4 and L1-5 results.

Statistical Analysis

Number Cruncher Statistical System (NCSS) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. The data was evaluated using descriptive statistical methods, and the Shapiro-Wilk Test was used to assess the distribution. A comparison of the three and above groups with a normal distribution of quantitative data was performed using the ANOVA test, and the Mann-Whitney U Test was used to compare the differences between the three and above groups. The cut-off value of quantitative data was determined with ROC analysis. Significance was evaluated at p <0.01 and p <0.05 levels.

Results

This study included 67 women and 32 men aged 40–79. The HU values of patients were classified into four groups. Average HU values decreased consistently over the ten years at the compared vertebral levels (Fig. 1). The differences were statistically significant (p <0.05). The subgroup analysis showed no significant difference between the vertebrae in the age groups (p>0.05). However, there were significant differences between the age groups (p <0.05) (Table 1). There was a considerable decrease in HU values between the 50 s age group and the 60 s age group (p <0.05). There was no significant difference in HU value between genders (p>0.05). There was no difference between the lumbar region vertebrae regarding HU values (p>0.05). When the values obtained from L1-4 and HU obtained from L1-5 were compared, the differences were insignificant (p>0.05). The HU values obtained from our study tended to decrease with age, and BMD decreased (Fig. 2).

Table 1. *Comparison of HU values between age groups*

		N	mean ± standard deviation	%95 confidence interval	p
40–49 age group	L-1	22	185.86±15.6	178.94–192.78	0.319
	L-2	22	184.95±16.16	177.78–192.12	
	L-3	22	190.36±17.09	182.78–197.94	
	L-4	22	194.91±13.76	188.80–201.00	
	L-5	22	197.14±26.63	185.32–208.94	
	L-1–4	22	189.05±14.72	182.51–195.57	
	L-1–5	22	190.65±16.35	183.39–197.89	
50–59 age group	L-1	31	170.71±29.61	159.84–181.57	0.329
	L-2	31	166.19±36.55	152.78–179.60	
	L-3	31	152.06±30.75	140.78–163.34	
	L-4	31	159.19±30.44	148.02–170.36	
	L-5	31	170.52±38.19	156.50–184.52	
	L-1–4	31	162.07±29.84	151.12–173.01	
	L-1–5	31	163.74±28.51	153.27–174.19	
60–69 age group	L-1	30	117.13±24.19	108.10–126.16	0.544
	L-2	30	114.57±23.72	105.71–123.42	
	L-3	30	108.57±21.75	100.44–116.68	
	L-4	30	115.07±24.85	105.78–124.34	
	L-5	30	118.87±25.29	109.42–128.31	
	L-1–4	30	113.86±20.94	106.04–121.68	
	L-1–5	30	114.84±21.07	106.97–122.70	
70–79 age group	L-1	16	96.19±25.4	82.65–109.72	0.563
	L-2	16	89.94±30.28	73.80–106.07	
	L-3	16	92.13±30.82	75.70–108.54	
	L-4	16	104.56±37.2	84.73–124.38	
	L-5	16	108.06±31.97	91.02–125.09	
	L-1–4	16	95.69±25.72	81.98–109.39	
	L-1–5	16	98.18±25.83	84.4–111.93	
Kruskall-Wallis Test	*p<0.05		**p<0.01		

A significant difference was found between the L1–4 values according to the groups (p <0.001). The L1–4 value of the group with normal HU value was statistically significant compared to the group with osteopenic and osteoporosis (p <0.001). In addition, the L1–4 value of the osteopenic group was higher than that of the osteoporosis group (p <0.001).

A significant difference was found between the groups' HU values of L1–5 vertebrae (p=0.001; p <0.01). The L1–5 value of the group with normal HU values was higher than the group with osteopenic and osteoporosis statistically significant (p=0.001; p <0.01). The L1–5 value of the osteopenic group was higher than that of the osteoporosis group (p=0.001; p <0.01).

The optimal cut-off value was calculated with the ROC curve to estimate osteopenia and osteoporosis using the HU value.

When the cut-off point of the L1–4 measurement was taken as 127.55, the sensitivity was determined as 93.7%, and the specificity as 99% as the reliable cut-off value. When the cut-off point of the L1-4 measurement was 76.9, sensitivity was determined as 98.8%, and specificity as 99% as a reliable cut-off value. When the cut-off point of the L1-5 measurement was taken as 125.5, sensitivity was determined as 98.4% and specificity as 93.7% as a reliable cut-off value. When the cut-off point of the L1-5 measurement was taken as 78.7, sensitivity was determined as 99.8%, and specificity was defined as a reliable cut-off value as 99.7%.

When the DEXA results of the patients were examined, the average T scores of 99 patients ranged from -3.4 to +2.8. Correlations of HU value with T score were significant (p <0.001).

According to the guidelines of the World Health Organization, the lumbar vertebrae T-score of 99 patients was divided into three groups: normal (-1.0 or greater), osteopenic (less than -1.0 and greater than -2.5), and osteoporotic (–2.5 or less) (Table 2). Average HU values of patients in normal, osteopenic, and osteoporotic groups were 168.57±27.64, 101.98±11.16, and 61.78±12.39 HU according to L1-4. According to L1-5, it was 169.57±28.13 normal, 104.86±12.9 osteopenic, 61.8±12.3 osteoporotic HU (Table 3). The differences in mean HU values between the groups were significant (p <0.001).

A post-hoc power analysis was performed to calculate the power obtained using the current findings of the study. The mean L1-4 measurement was calculated as 168.57±27.64 in the patient group with normal HU, 101.98±11.16 in osteopenic patients, and 61.78±12.39 in osteoporotic patients. The corresponding effect size value was determined as f=2.45. Still, it was accepted as the upper limit of the effect size value. The value of f=0.40 was taken into account. Considering the relevant effect size value, the power value obtained from our study, where the type I error was accepted as 5%, was determined as 95%, with a total of n=99 units, and the analyses were analyzed by G*Power has been made[10].

Table 2. *Normal, osteopenic, and osteoporotic values according to HU values*

T score	mean ± standart deviation	95 confidence interval	p
L1–4			
Normal (≥ -1.0)	168.57±27.64	161.60–175.52	0.001
Osteopenic (<-1.0 or > -2.5)	101.98±11.16	97.95–105.99	0.001
Osteoporotic (≤ -2.5)	61.78±12.39	42.05–81.49	0.001
L1–5			
Normal (≥ -1.0)	169.57±28.13	134.34–151.10	0.001
Osteopenic (<-1.0 or > -2.5)	104.86±12.9	100.21–109.51	0.001
Osteoporotic (≤ -2.5)	61.8±12.3	42.22–81.37	0.001

Table 3. *Comparison of normal, osteopenic, and osteoporotic HU values*

	Normal	Osteopenic	Osteoporotic
Bredow et al.[23]	120.80±41.80	78.80±23.00	54.70±25.20
Choi et al.[10]	167.90±47.20	109.70±28.90	80.40±38.70
Schreiber et al.[9]	133.00±37.60	100.80±24.50	78.50±32.40
Current study	168.57±27.64	101.98±11.16	61.78±12.39

Discussion

In surgical procedures where fusion is aimed by spinal instrumentation, osteoporosis is one of the leading causes of surgical failure[11,12]. Identifying the osteoporosis before fusion surgery is very important.

Dual X-ray absorptiometry is the gold standard for evaluating BMD[2,12–14]. However, patients with severe degeneration, aortic calcification, and obesity may have false normal BMD values[12,15–17].

Bone mineral density can also be measured using CT. Patients of various age groups, regardless of gender, can be evaluated at no additional cost. Quantitative CT only provides true volumetric Bone Mineral Density measurement (mg/ cm^3). Unlike DEXA, cortical and trabecular bone can be analyzed separately. Computed tomography is more sensitive than DEXA in predicting vertebral fractures and monitoring bone loss. The main advantage of DEXA is that it excludes the measurement of structures that do not contribute to the mechanical resistance of the spine and selectively measures the trabecular bone. It is not affected by extra-bone calcifications. Computed tomography is useful for monitoring BMD changes in patients with structural abnormalities that prevent the use of DEXA in their spine (scoliosis, etc.). However, CT cannot be used in WHO diagnostic classification criteria. Computed tomography has several limitations, such as the high cost and the risk of high radiation exposure. Therefore, CT is not widely used in clinical practice in estimating osteoporosis, but it is routinely used in surgical planning[12,18,19].

The National Osteoporosis Foundation recommends that the lowest T-score for the L1-L4 lumbar vertebra, total proximal femur, or femoral neck should be evaluated for the diagnosis of osteoporosis[1,20]. In our study, we used the HU values obtained from L1–4 and L1-L5 and found a correlation with the DEXA values of the patients. We found 98.8% sensitivity and 99% specificity in CT. The cut-off value of this study shows that HU values are sensitive and specific for screening osteopenia and osteoporosis.

Patients with lumbar spinal instrumentation and those with secondary diseases such as spinal fracture, spinal tumor, spondylopathy, and systemic disease that may affect BMD may also give false results.

In spinal fusion surgery, trabecular bone density is significant in the success of instrumentation. Dual X-ray absorptiometry evaluates trabecular and cortical bone, but only trabecular bone density is calculated. At the same time, HU values are obtained from CT. Planning the spinal fusion operation according to HU values will increase success.

Türkyilmaz et al. used HU values for implant surgery in dentistry to detect the regional oral BMD[21]. Metal torques are highly correlated with insertion torque and stability of metal implants[22]. Hounsfield unit value can be an important prognostic factor in implant stability for any bone region in dentistry. Measuring the value of HU in the planned screw trajectory can be used to estimate the strength of the bone-screw interface. We think the measurement of HU can be useful in predicting fusion success before spine fusion surgery.

Zou et al. investigated the relation between screw loosening and HU in patients with pedicular screws. They demonstrated that the HU values measured on CT are an independent determinant for loosening the pedicle screw and that the low HU value is significantly correlated with the higher risk of loosening[23]. Bredow and Schwaiger also achieved similar results in their studies[24,25]. Some researchers reported that the fusion rate was considerably higher in patients with high HU values, and low HU values paved the way for developing pseudoarthrosis[23–26].

In our study, there was a maximum time gap of 6 months between CT and DEXA that can affect the study results. However, we exclude those who have medical treatment for osteoporosis and those with an endocrine disease that affects BMD, so this may be a low probability.

The significant limitations of this study are its retrospective nature and the relatively small number of patients in this series.

Conclusion

Hounsfield unit values obtained from lumbar CT significantly correlates with BMD based on DEXA scanning. This study obtained valid HU values for diagnosing healthy individuals, osteopenia, and osteoporosis.

Conflict of Interest

The authors declare no conflict of interest.

Funding

No funding.

References

1. Bulut G, Aytar MH, Güngör A. Surgıcal prıncıples ın posterıor transpedıcular screw fıxatıon and fusıon for treatment of spondylolısthesıs: Retrospectıve evaluatıon of 77 cases. The J of Turkish Spinal Surg. 2019;30:111–6.
2. Ebbesen EN, Thomsen JS, Beck-Nielsen H, Nepper-Rasmussen HJ, Mosekilde L. Lumbar vertebral body compressive strength evaluated by dual-energy X-ray absorptiometry, quantitative computed tomography, and ashing. Bone. 1999;25:713–24.
3. Masud T, Langley S, Wiltshire P, Doyle DV, Spector TD. Effect of spinal osteophytosis on bone mineral density measurements in vertebral osteoporosis. BMJ. 1993;307:172–3.
4. Prevention and management of osteoporosis World Health Organ Tech Rep Ser. 2003;921:1–164.
5. Adams JE. Quantitative computed tomography. Eur J Radiol. 2009;71:415–24.
6. Link TM, Koppers BB, Licht T, Bauer J, Lu Y, Rummeny EJ. In vitro and in vivo spiral CT to determine bone mineral density: initial experience in patients at risk for osteoporosis. Radiology. 2004;231:805–11.
7. Papadakis AE, Karantanas AH, Papadokostakis G, Petinellis E, Damilakis J. Can abdominal multi-detector CT diagnose spinal osteoporosis? Eur Radiol. 2009;19:172–6.
8. Tay WL, Chui CK, Ong SH, Ng AC. Osteoporosis screening using areal bone mineral density estimation from diagnostic CT images. Acad Radiol. 2012;19:1273–82.
9. Schreiber JJ, Anderson PA, Rosas HG, Buchholz AL, Au AG. Hounsfield units for assessing bone mineral density and strength: a tool for osteoporosis management. J Bone Joint Surg Am. 2011;93:1057–63.
10. Foul F, Erdfelder E, Lang AG, Buchner A. Using G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior Research Methods. 2007;39, 175–191.
11. Choi MK, Kim SM, Lim JK. Diagnostic efficacy of Hounsfield units in spine CT for the assessment of real bone mineral density of degenerative spine: correlation study between T-scores determined by DXA scan and Hounsfield units from CT. Acta Neurochir (Wien) 2016;158:1421–7.
12. Kim JK, Kim DH, Lee JI, Choi BK, Han IH, Nam KH. Hounsfield Units on Lumbar Computed Tomography for Predicting Regional Bone Mineral Density. Open Med (Wars) 2019;14:545–51.
13. Cauley JA, Lui LY, Ensrud KE, Zmuda JM, Stone KL, Hochberg MC. Bone mineral density and the risk of incident nonspinal fractures in black and white women. JAMA. 2005;293:2102–8.
14. Damilakis J, Maris TG, Karantanas AH. An update on the assessment of osteoporosis using radiologic techniques. Eur Radiol. 2007;17:1591–602.
15. Lochmuller EM, Burklein D, Kuhn V, Glaser C, Muller R, Gluer CC. Mechanical strength of the thoracolumbar spine in the elderly: prediction from in situ dual-energy X-ray absorptiometry, quantitative computed tomography (QCT), upper and lower limb peripheral QCT, and quantitative ultrasound. Bone. 2002;31:77–84.
16. Nguyen ND, Eisman JA, Center JR, Nguyen TV. Risk factors for fracture in nonosteoporotic men and women. J Clin Endocrinol Metab. 2007;92:955–62.
17. Yu EW, Thomas BJ, Brown JK, Finkelstein JS. Simulated increases in body fat and errors in bone mineral density measurements by DXA and QCT. J Bone Miner Res. 2012;27:119–24.
18. Genant HK, Block JE, Steiger P, Glueer CC, Smith R. Quantitative computed tomography in assessment of osteoporosis. Semin Nucl Med. 1987;17:316–33.
19. Liu CC, Theodorou DJ, Theodorou SJ, Andre MP, Sartoris DJ, Szollar SM. Quantitative computed tomography in the evaluation of spinal osteoporosis following spinal cord injury. Osteoporos Int. 2000;11:889–96.
20. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of postmenopausal osteoporosis Endocr Pract 16(Suppl 3);2010.
21. Turkyilmaz I, Aksoy U, McGlumphy EA. Two alternative surgical techniques for enhancing primary implant stability in the posterior maxilla: a clinical study including bone density, insertion torque, and resonance frequency analysis data. Clin Implant Dent Relat Res. 2008;10:231–7.
22. Turkyilmaz I, Sennerby L, McGlumphy EA, Tozum TF. Biomechanical aspects of primary implant stability: a human cadaver study. Clin Implant Dent Relat Res. 2009;11:113–9.
23. Zou D, Muheremu A, Sun Z, Zhong W, Jiang S, Li W. Computed tomography Hounsfield unit-based prediction of pedicle screw loosening after surgery for degenerative lumbar spine disease. J Neurosurg Spine. 2020;1–6.
24. Bredow J, Boese CK, Werner CML, Siewe J, Löhrer L, Zarghooni K, et al. Predictive validity of preoperative CT scans and the risk of pedicle screw loosening in spinal surgery. Arch Orthop Trauma Surg. 2016;136:1063–7.
25. Schwaiger BJ, Gersing AS, Baum T, Noël PB, Zimmer C, Bauer JS. Bone mineral density values derived from routine lumbar spine multidetector row CT predict osteoporotic vertebral fractures and screw loosening. AJNR Am J Neuroradiol. 2014;35:1628–33.
26. Schreiber JJ, Hughes AP, Taher F, Girardi FP. An association can be found between Hounsfield units and success of lumbar spine fusion. HSS J. 2014;10:25–9.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Is the John Thomas Sign a Finding Indicating the Direction of a Pelvis Fracture?

John Thomas İşareti Pelvis Kırığının Yönünü Gösteren Bir Bulgu mudur?

Emre Karsli[1], Murat Aras[2]

[1]Department of Emergency Medicine, Cigli Regional Training Hospital, Izmir; [2]Department of Emergency Medicine, Inegol State Hospital, Bursa, Türkiye

ABSTRACT

Introduction: *The John Thomas (JT) sign is defined as the penis showing the direction of the fracture in hip or pelvic fractures in male patients. The sensitivity and specificity values of the John Thomas sign vary widely in studies.*

Materials and Methods: *Male patients over the age of 18 who applied to the Emergency Department of the Faculty of Medicine of Kafkas University between 01.01.2015 and 14.10.2020 due to trauma and who had pelvic tomography were included in the study. The study included 118 male patients who had fractures in the pelvis, proximal femur, and femoral shaft as a result of tomography and 73 male individuals who applied for trauma and had pelvic tomography but did not have any abdominal, pelvis, or lower extremity injuries. The penis angle was recorded as the intersection angle of the vertical line drawn from the symphysis pubis and the line drawn from the midline of the penis corpus cavernosum to the tip of the penis. The study did not include individuals with pelvic asymmetry and those with previous pelvic surgery.*

Results: *The mean age of the patient group was 45.2±6.4 years, and the mean age of the control group was 44.9±5.9 years. There was no statistically significant difference between the mean ages of the groups (p=0.557. While 52 (83.9%) of 62 patients with fractures on the left side of the pelvis had positive JT sign, 37 (66.1%) of 56 patients with right-side fractures had positive JT sign. There was a moderate correlation between fracture and penile direction in the patient group (p=0.0001, rho=0.509).*

Conclusion: *As a result of our study, it was determined that the John Thomas sign alone is not sufficient to detect pelvic fractures, but it can help to diagnose patients with pelvic trauma and suspected fractures.*

Keywords: *John Thomas sign; Throckmorton sign; pelvic fractures; Solooki signKey words: John Thomas sign; Throckmorton sign; pelvic fractures; Solooki sign*

ÖZET

Giriş: *John Thomas (JT) bulgusu erkek hastalarda, kalça ya da pelvis kırıklarında penisin kırığın yönünü göstermesi olarak tanımlanır. Yapılan araştırmalarda John Thomas bulgusunun sensitivite ve spesifite değerleri geniş aralıkta değişmektedir.*

Materyal Metod: *Kafkas Üniversitesi Tıp Fakültesi Acil Servisine 01.01.2015–14.10.2020 tarihleri arasında travma sebepli başvurmuş ve pelvis tomografisi çekilmiş 18 yaş üzeri erkek hastalar çalışmaya dâhil edildi. Çalışmaya çekilen tomografi sonucunda pelvis kemiklerinde, femur proksimalinde ve femur şaftında fraktür saptanmış olan 118 erkek hasta ile travma sebepli başvurup pelvis tomografisi çekilmiş, herhangi batın, pelvis veya alt ekstremite yaralanması saptanmamış 73 erkek birey dâhil edildi. Penis açısı symphisis pubisten çizilen dikey hat ile penis corpus cavernosum orta hattından penis ucuna çizilen çizginin kesişim açısı olarak kaydedildi. Pelvik asimetrisi mevcut olan bireyler ve önceden pelvis cerrahisi geçirmiş olan bireyler çalışmaya dâhil edilmedi.*

Bulgular: *Hasta grubun yaş ortalaması 45,2±6,4 yıl, kontrol grubunun yaş ortalaması ise 44,9±5,9 olarak saptandı. Grupların yaş ortalamaları arasında istatistiksel olarak anlamlı farklılık saptanmadı (p=0,557). Pelvisin sol tarafında fraktür saptanan 62 hastanın 52 (%83,9)'sinde JT bulgusu pozitifken, sağ tarafında fraktürü olan 56 hastanın 37'sinde (%66,1) JT bulgusu pozitif olarak saptandı. Hasta grubunda fraktür yönü ve penis yönü arasında orta derecede korelasyon saptandı (p=0,0001, rho=0,509).*

Sonuç: *Çalışmamız sonucunda John Thomas bulgusunun pelvik fraktürleri tek başına tespit etmede yeterli olmadığı fakat pelvis travması olan ve fraktürden şüphelenilen hastalarda tanı koymada yardımcı olabileceği saptanmıştır.*

Anahtar kelimeler: *John Thomas işareti; Throckmorton işareti; pelvik kırıklar; Solooki işareti*

İletişim/Contact: *Emre Karsli, Cigli Regional Training Hospital, Department of Emergency Medicine, Izmir, Türkiye* • ***Tel:*** *0505 513 37 44* • ***E-mail:*** *dremrekarsli@gmail.com* • ***Geliş/Received:*** *16.08.2022* • ***Kabul/Accepted:*** *15.03.2024*

ORCID: *Emre Karslı: 0000-0002-0441-3019* • *Murat Aras: 0000-0002-4329-4147*

Kafkas J Med Sci 2024; 14(1):14–18
doi: 10.5505/kjms.2024.91568

Introduction

The pelvis is an important junctional region of the body that connects vascular and neuronal structures, especially the gastrointestinal and gastro-urinary systems[1,2]. Studies show that although pelvic fractures constitute 1–3% of all fractures, the incidence of pelvic fractures may increase up to 20% in patients with multiple traumas due to their connection with many systems. Despite current medical approaches, pelvic fractures are a significant cause of mortality and morbidity[3,4]. Every year, approximately one-third of the population aged 65 and over falls, and this rate rises to 50% over the age of 80[5]. Hip fracture is suspected in 75000 patients every year in the United Kingdom, and the annual cost of these patients is estimated to be approximately 2 billion pounds[6].

Early treatment of hip fractures reduces hospital stays and helps with pain control. However, it is accepted that 2–10% of fractures may not be visible on initial radiographs, and further imaging is required to make a definitive diagnosis. These fractures are called occult hip fractures[7]. This situation has led clinicians to seek additional signs for suspicious cases.

The John Thomas (JT) sign is defined as the penis showing the direction of the fracture in hip or pelvic fractures in male patients. Few studies have determined its diagnostic value objectively[8].

This finding is named after Thomas "Tom" Bentley Throckmorton, a neurologist and Iowa president of the American Medical Association[8]. This is called the "Solooki Sign" in Iran[9] and the "Oram Sign" in Scandinavia[10].

The sensitivity and specificity values of the John Thomas sign vary widely in studies. Additional studies on this sign are needed, as some suggest an 'over chance' relationship between the JT sign and unilateral hip fracture[8].

The definitive diagnosis of suspected hip fractures can be made more easily in centers with computerized tomography (CT) or magnetic resonance imaging (MRI). However, physicians have to decide only with physical examination and radiography in centers where these imaging facilities are unavailable or cannot be performed due to the patient (such as implants). In our study, we investigated whether the John Thomas sign is an additional finding to facilitate the diagnosis of hip fractures.

Material and Method

Male patients over the age of 18 who applied to the Emergency Department of the Faculty of Medicine of Kafkas University between 01.01.2015 and 14.10.2020 due to trauma and who had a pelvic tomography were included in the study. One hundred eighteen male patients with fractures in the pelvic bones, proximal femur, and femoral shaft as a result of tomography and 73 male individuals who applied for trauma and had a pelvic tomography without any abdominal, pelvic, or lower extremity injuries were included. The age, gender, location of the pelvic fracture, penile direction, and penile shaft angle of the patient group were recorded in the data set. In the control group, age, gender data, penile direction, and penile shaft angle were recorded in the data set. The study did not include individuals with pelvic asymmetry and those with previous pelvic surgery (46 patients).

Penile Direction and Penile Angle Measurement

While determining penile direction and angle, a vertical line (line a) was drawn down from the symphysis pubis level in the scenogram imaging of pelvis CT. The area was divided into two areas, right and left. The half area where the glans penis stood was recorded in the data set (Fig. 1, line a).

Another line (line b) was drawn from the glans penis to the dorsum penis. The angle α, where the line between the glans penis and the dorsum penis intersects the vertical line from the symphysis pubis, was determined as the penile angle (Fig. 1).

Statistical Analysis

The power analysis we performed before the study determined that 110 people (at least 55 for each group) were needed, assuming that the estimated effect size would be medium-high (f=0.65) to 95% power at the 95% confidence interval. The IBM Statistical Package for Social Sciences (SPSS) package program was used to analyze the dataset obtained from the study.

Mean ± standard deviation or median (IQR) gave continuous variables. Sample size frequencies were used to provide categorical variables. The normality of the parameters' distribution was analyzed using the Kolmogorov-Smirnov test.

Relations between the categorical variables were analyzed by using the chi-square test. Independent

nonparametric group comparisons were analyzed by using the Mann-Whitney U test. Spearman's correlation test was used to investigate correlations between the fracture side and penile angle. Binary logistic regression analysis was used to analyze the factors that affect JT sign positivity. The significance level for all analyses was determined as $p < 0.05$.

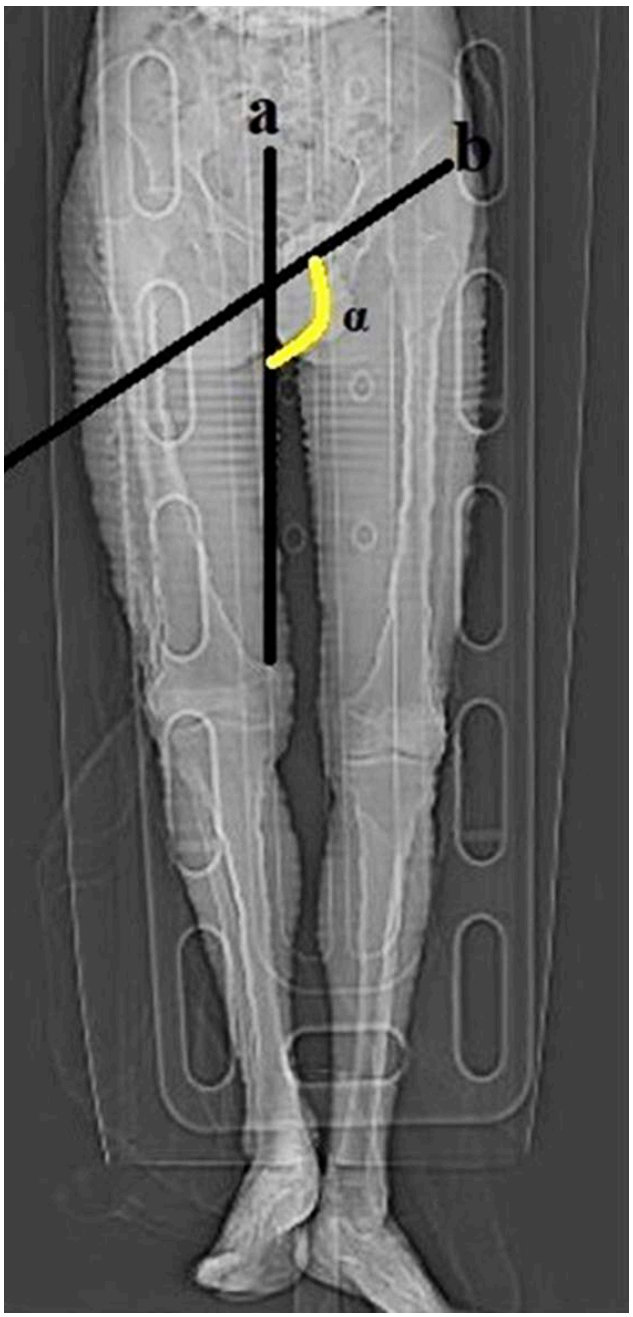

Figure 1. *Scenogram of pelvic CT image. Line a is a vertical line drawn down from the symphysis pubis level, and line b is an oblique line drawn from the glans penis to the dorsum penis. The angle α, where the line between the glans penis and the dorsum penis intersects the vertical line from the symphysis pubis, was determined as the penile angle.*

Results

The mean age of the patient group was 45.2±6.4 years, and the mean age of the control group was 44.9±5.9 years. There was no statistically significant difference between the mean ages of the groups (p=0.557). In the patient group, 68 (57.6%) patients had femoral neck-trochanter region fractures, 26 (22%) patients had femoral shaft fractures, and 24 (20.3%) patients had fractures of other pelvic bones (Table 1).

Eighty-nine (75.42%) patients had positive JT signs, and 29 (24.58%) patients had negative JT signs. There was no statistically significant difference in penile direction distribution in patients with and without JT sign and the control group (p=0.17) (Table 1).

Considering the penile shaft angles, it was 42.2 (12.9–56.85) degrees in the control group and 37.5 (16.22–91.52) in the patient group. There was no statistically significant difference between the groups regarding penile shaft angles (p=0.646) (Table 1).

Considering the penile direction, 71 (60.2%) patients had the penis in the left direction; 47 (39.1%) people had the right direction in the patient group. In the control group, 53 (72.6%) people had the left direction, and 20 (27.4%) had the right direction. There was no statistically significant difference between the patient and control groups in terms of penile direction (p=0.088) (Table 1).

While 52 (83.9%) of 62 patients with fractures on the left side of the pelvis had positive JT sign, 37 (66.1%) of 56 patients with right-sided fractures had

Table 1. *Clinical data of the groups*

	Patient group (n=118)	Control group (n=73)	p-value
Age, median ± sd	45.2±6.4	44.9±5.9	
Fracture area			
Femoral neck-trochanter, N (%)	68 (57.6%)		
Femoral shaft, N (%)	26 (22%)		
Other, N (%)	24 (20.3%)		
JT sign			
Positive	89 (75.42%)		
Negative	29 (24.58%)		
Penis shaft angel median (IQR)	37.5 (16.22–91.52)	42.2 (30.35–56.85)	0.646
Penile direction, N (%)			
Left	71 (60.2%)	53 (72.6%)	0.088
Right	47 (39.1%)	20 (27.4%)	

Table 2. *Clinical data of the subgroups*

	JT (+) Subgroup (n=62)	JT (-) Subgroup (n=56)	p-value	Correlation coefficients
Fracture area				*p=0.0001 *rho=0.509
Femoral neck-trochanter, N (%)	53 (77.9%)	15 (22.1%)	0.247	
Femoral shaft, N (%)	21 (80.8%)	5 (19.2%)		
Other, N (%)	15 (62.5%)	9 (37.5%)		
Penis shaft angel median (IQR)	31 (15.05–89.6)	53 (34.25–93)	0.082	
Penile direction, N (%)				
Left	52 (58.42%)	19 (65.51%)	0.272	
Right	37 (41.58%)	10 (34.49%)		
Fracture sides		*		
Left	52 (83.9%)	10 (16.1%)	0.032	
Right	37 (66.1%)	19 (33.9%)		

*p-value and rho value are derived from the Spearman correlation test.
p values are derived from the chi-square test.

Table 3. *Logistic regression about factors which are related to John Thomas sign positivity*

	B	S. E.	Wald	p-value	OR (95%CI for OR)
Age	-0.002	0.015	0.018	0.892	0.998 (0.968–1.028)
Fracture area	-0.630	0.550	1.314	0.252	0.532 (0.181–1.564)
Fracture_side	-1.420	0.541	6.888	0.009	0.242 (0.084–0.698)
Penil direction	1.089	0.548	3.947	0.047	0.336 (0.115–0.985)
Penil shaft angle	0.004	0.005	0.542	0.462	1.004 (0.994–1.014)

negative JT sign. The JT sign positive subgroup includes patients with left side fracture more than the JT sign negative subgroup (p=0.032). Also, there was a moderate correlation between the fracture side and penile direction in the patient group (p=0.0001 and rho=0.509) (Table 2).

While the JT sign was positive in 53 (77.9%) of 68 patients with femoral head, neck-trochanter region fractures, the JT sign was found in 21 (80.8%) of 26 patients with femoral shaft fractures and 15 (62.5%) of 24 patients with fractures in other pelvic bones (Table 2).

When the factors affecting the JT sign positivity in the patient group were examined, it was determined that the fracture direction and penile direction had an effect on the JT sign positivity in the patient group (p=0.009, OR=0.242 and p=0.047, OR=0.336 respectively) (Table 3).

Discussion

At the end of our study, we found the JT sign to be positive in the range of 66–83.9% in hip fracture cases. In the literature, there are different values regarding the positivity of the JT finding in studies on this subject. In the study of Murphy et al.[8], the JT sign was positive, with a rate of 46%.

Gerber et al.[11], on the other hand, stated that although they found 75.7% sensitivity in determining the side of a fracture when a fracture is present in their meta-analysis compiled from 9 articles published on the JT finding, the results of the meta-analysis could not determine the laterality of the fracture with any degree of certainty.

Although the JT sign is positive in the range of 66–83.9% in the patient group, the lack of penile direction difference between the general population and the patient group suggests that the JT finding may be due to a unilateral point of view.

Although radiography is the first-choice imaging method in the emergency department, it can miss 4–14% of fractures in the emergency room population. This rate is higher in the elderly population (39–44)[12]. As a result of our study, the JT sign in pelvis fractures was found to be positive in the range of 66–83.9%, depending on the location of the fracture. According to these results, JT findings should also be considered for diagnosis in elderly patients with suspected pelvic fractures, especially in emergency services where there is no imaging other than radiography.

In the study of Gill et al.[7] on using MRI and CT in occult hip fractures, 1353 patients were examined. Advanced imaging studies were performed in 92 of

the patients with the suspicion of occult hip fracture. Occult hip fractures were found in 34 of these patients. Occult hip fracture was detected in 2.5% of the patients included in the study. When the results of our research are evaluated together with the data in the literature, even if the JT finding is weak, it may be suggestive in detecting the location of occult fractures.

Skura et al.[13] investigated the ability of JT findings to predict orthopedic pathologies in orthopedic trauma patients. The mean patient age of the study, which included 360 male patients, was 42, close to our study (range 18–91 years). As a result of the study, although the relative risk ratio of the JT finding was found to be 4.24, similar to our study, it was determined that the JT sign could not be used alone as a diagnostic tool but could be used as an additional diagnostic tool.

Conclusion

As a result of our study, it was determined that the John Thomas sign alone is not sufficient to detect pelvic fractures but may help in the diagnosis of patients with pelvic trauma and suspected fractures.

References

1. Spencer Tomberg, Austin Heare. Pelvic trauma: Initial evaluation and management. https://www.uptodate.com/contents/pelvic-trauma-initial-evaluation-and-management#:~:text=Incidence%20and%20mortality%20%E2%80%94%20Pelvic%20fractures,percent%20%5B2%2C3%5D. Accessed 10.08.2022
2. Grotz MR, Allami MK, Harwood P, Pape HC, Krettek C, Giannoudis PV. Open pelvic fractures: epidemiology, current concepts of management and outcome. Injury. 2005;36(1):1–13.
3. Costantini TW, Coimbra R, Holcomb JB, Podbielski JM, Catalano R, Blackburn A, et al. Current management of hemorrhage from severe pelvic fractures: Results of an American Association for the Surgery of Trauma multi-institutional trial. J Trauma Acute Care Surg. 2016;80(5):717–23;discussion 723–5.
4. Balogh Z, King KL, Mackay P, McDougall D, Mackenzie S, Evans JA, et al. The epidemiology of pelvic ring fractures: a population-based study. J Trauma. 2007;63(5):1066–73;discussion 1072–3.
5. C. A. Pfortmueller, M. Kunz, G. Lindner, A. Zisakis, S. Puig, A. K. Exadaktylos, Fall-related emergency department admission: fall environment and settings and related injury patterns in 6357 patients with special emphasis on the elderly, Sci World J. 2014;2014:256519.
6. National Clinical Guideline Centre (UK). The Management of Hip Fracture in Adults [Internet]. London: Royal College of Physicians (UK) ;2011. PMID:22420011.
7. Gill SK, Smith J, Fox R, Chesser TJ. Investigation of occult hip fractures: the use of CT and MRI. ScientificWorldJournal. 2013;2013:830319.
8. Murphy IG, Murphy CG, Heffernan EJ. John Thomas sign--a memorable but misleading sign in hip fractures. Orthop Traumatol Surg Res. 2014;100(2):199–202.
9. Solooki S., Vosoughi A. R. John Thomas Sign: is it helpful to determine the lower limb fracture? Pakistan J Radiol. 2010:134–135.
10. Brink O, Borris LC, Andersen K, Hougaard K. [Oram's sign for hip or pelvic disorder]. (2009)Ugeskrift for laeger. 171(51):3760–3.
11. Gerber L, Laher AE, Enyuma COA, et al. The 'John Thomas' sign and pelvic fractures-Fact or humorous myth?: A systematic review and meta-analysis. J Clin Orthop Trauma. 2019;10(1):161–166.
12. Ellen X. Sun, Jacob C. Mandell, Michael J. Weaver, Vera Kimbrell, Mitchel B. Harris, Bharti Khurana, Clinical utility of a focused hip MRI for assessing suspected hip fracture in the emergency department, Emerg Radiol. 2021;28(2):317–325.
13. Skura B, Ebaugh MP, Passias BJ, DeGenova D, Hoffman A, Scheschuk J, Taylor BC. Pelvic Shadowing as a Diagnostic Predictor of Orthopedic Pathology in Orthopedic Trauma Patentse. Cureus. 2021;13(9):e17873.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of Nutritional Status of Fibromialgia Patients

Fibromiyalji Hastalarında Beslenme Durumunun Değerlendirilmesi

Hakan Toguc[1], Murat Toprak[2]

[1]Department of Nutrition and Dietetics, Faculty of Health Sciences, Inonu University, Malatya; [2]Department of Physiotherapy and Rehabilitation, Faculty of Medicine, Van Yuzuncu Yil University, Van, Türkiye

ABSTRACT

Aim: *Fibromyalgia syndrome is a multifactorial health problem that often develops with widespread pain in the skeletal and muscular systems. It is thought that nutrition, diet therapy, and the treatment methods used for the disease may be adequate. This study aims to evaluate the food consumption and anthropometric measurements (body weight, height, body mass index) of patients with fibromyalgia syndrome.*

Material and Method: *This study was conducted with 100 female individuals with a mean age of 33.7±6.4 years, diagnosed with fibromyalgia, who applied to the Van Training and Research Hospital, Physical Therapy and Rheumatology Department Polyclinics. A questionnaire form (containing data on socio-demographic information, dietary habits, and anthropometric measurements) was applied to the participants who accepted the study using the researcher's face-to-face interview technique.*

Results: *While the majority of the participants were housewives (72%), it was determined that 93% of the participants had fatigue and muscle pain, and 91% had sleep disorders. Body mass index (BMI) was 25.0–29.9 kg/m² in 59% of the participants and 30.0–39.9 kg/m² in 8%. It was determined that there was a significant difference between the BMIs of the individuals with the symptoms of fibromyalgia depression (p<0.001), anxiety (p<0.001), and fatigue (p=0.011).*

Conclusion: *To reduce the disease's symptoms and increase the quality of life during the fibromyalgia treatment phase, individuals should be directed to dietitians, and anthropometric measurements should be considered when evaluating their nutritional status.*

Key words: *fibromyalgia syndrome; nutrition; obesity; anthropometric measurements*

ÖZET

Amaç: *Fibromiyalji sendromu, sıklıkla iskelet ve kas sistemlerinde gözlenen yaygın ağrı ile gelişen multifaktöriyel bir sağlık sorunudur. Hastalığa ilişkin kullanılan tedavi yöntemleri ile beraber beslenme ve diyet tedavisinin etkili olabileceği düşünülmektedir. Bu araştırmada fibromiyalji sendromuna sahip hasta bireylerin besin tüketimlerinin ve antropometrik ölçümlerinin (vücut ağırlığı, boy uzunluğu, beden kütle endeksi) değerlendirilmesi amaçlanmaktadır.*

Materyal ve Metot: *Bu araştırma Van Eğitim ve Araştırma Hastanesi Fizik Tedavi ve Romatoloji Bölümü Poliklinikleri'ne başvuran fibromiyalji tanısı almış, 33,7±6,4 yıl yaş ortalamalarına sahip olan 100 kadın birey ile gerçekleştirilmiştir. Araştırmayı kabul eden katılımcılara anket formu (sosyo-demografik bilgiler, beslenme alışkanlıkları ve antropometrik ölçümlerine ilişkin veriler içeren) araştırmacı tarafından yüz yüze görüşme tekniği ile uygulanmıştır.*

Bulgular: *Katılımcıların büyük çoğunluğu ev hanımı (%72) iken, katılımcıların %93'ünde yorgunluk ve kas ağrısı, %91'inde uyku bozuklukları olduğu tespit edilmiştir. Katılımcıların %59'unda beden kütle endeksi (BKİ) 25,0–29,9 kg/m² ve %8'inde 30,0–39,9 kg/m² olduğu bulunmuştur. Bireylerin BKİ'lerinin fibromiyalji hastalık sempromlarından depresyon (p<0,001), anksiyete (p<0,001) ve yorgunluk (p=0,011) ile arasında anlamlı bir fark olduğu saptanmıştır.*

Sonuç: *Fibromiyalji tedavi aşamasında hastalık semptomlarında azalma ve yaşam kalitesinde artış sağlayabilmek amacıyla bireylerin diyetisyenlere yönlendirilmesi ve beslenme durumlarının değerlendirilirken antropometrik ölçümerin de dikkate alınması gerekmektedir.*

Anahtar kelimeler: *fibromiyalji sendromu; beslenme; obezite; antropometrik ölçümler*

İletişim/Contact: *Hakan Toguc, Department of Nutrition and Dietetics, Faculty of Health Sciences, Inonu University, Malatya, Türkiye* • ***Tel:*** *0507 362 51 00* • ***E-mail:*** *diyetisyenhakantoguc@gmail.com* • ***Geliş/Received:*** *20.12.2022* • ***Kabul/Accepted:*** *06.03.2024*

ORCID: *Hakan Toğuç: 0000-0002-8134-1151* • *Murat Toprak: 0000-0002-6490-4645*

Introduction

The term fibromyalgia is used to describe many pain complaints that are generally encountered in women, cannot be revealed by a clear pathology, and are not well localized. Fibromyalgia syndrome (FMS) is a chronic widespread pain syndrome characterized by chronic widespread musculoskeletal pain, fatigue, sleep disturbances, and many idiopathic pain symptoms[1].

Fibromyalgia syndrome (FMS), whose disease origin and treatment method are not yet fully known, significantly affects the quality of life of patients with many findings, such as sleep disorders, depression, chronic fatigue, and cognitive dysfunction accompanying multiple pain states. The effectiveness of most therapies for fibromyalgia is not strongly supported, with only a few treatments, like cognitive behavioral therapy, antidepressants, and central nervous system depressants, showing small but significant improvements in pain and quality of life[2,3].

The American College of Rheumatology (ACR) 2010 defined fibromyalgia as a widespread pain condition observed in 11–18 tender points and persisting for at least three months. In 2016, the ACR revised these criteria to improve diagnostic accuracy, combining physician and questionnaire criteria to minimize misclassification of regional pain disorders[4].

As a result of studies, the prevalence of FMS worldwide was between 0.5 and 5.8%. Recent literature review updates show that fibromyalgia prevalence in the general population ranges between 0.2 and 6.6%, and in women specifically, it varies between 2.4 and 6.8%[5].

With the increase in studies that strengthen the hypothesis that oxidative stress plays a role in the origin of FMS, the opinion of increasing the antioxidant level and content of the diet has emerged. Oxidative stress might play a critical role in FM pathophysiology, and various antioxidative procedures have been discussed to diminish fibromyalgia symptoms[6].

The emerging research on oxidative stress in fibromyalgia highlights the potential of dietary interventions. Oxidative stress, characterized by increased levels of prooxidative factors such as nitric oxide and lipid peroxidation, can exacerbate pain sensitization in fibromyalgia[7]. This understanding has led to a growing interest in nutrition as a complementary treatment approach. Antioxidant-rich diets, which counteract oxidative stress, are becoming a focus in managing fibromyalgia symptoms. Modifying dietary habits to include foods high in antioxidants, such as fruits, vegetables, nuts, and seeds, could play a crucial role in alleviating some symptoms of fibromyalgia[8].

This study aims to elucidate the dietary consumption patterns prevalent among individuals diagnosed with Fibromyalgia Syndrome. Additionally, it seeks to evaluate the alignment of specific anthropometric parameters, namely body weight, height, and body mass index (BMI), with the established normative values.

Materials and Methods

This study has been structured as an observational investigation. The requisite sample size for this research was determined utilizing the 'Sample Size Calculator' function provided by Rasoft software. An initial computation suggested a minimum of 81 participants, considering a 5% margin of error. This estimation was grounded on a group of 120 patients diagnosed with fibromyalgia who attended the outpatient clinic of the Physical Therapy and Rehabilitation Department at Van Training and Research Hospital in March 2018. Following this, in April 2018, the necessary minimum participant count was achieved with the enrollment of 100 individuals.

Participants were thoroughly briefed about the study, and due to its voluntary nature, detailed explanations were provided before obtaining informed consent. The consent form was meticulously read and signed by the participants who agreed to partake in the study.

The inclusion of the subjects in the study was subject to their consent, and data collection was carried out through direct, face-to-face interviews. In these interviews, the researcher used a questionnaire form meticulously prepared. The data collected covered various areas such as age, education level, employment status, time since fibromyalgia diagnosis, duration of treatment, comorbid conditions, use of medication and vitamin-mineral supplements, smoking and alcohol consumption habits, main and snack meal details, food intake frequency, eating out practices, physical activity level and anthropometric measurements (height, weight, and BMI).

The inclusion criteria for the study were stringently defined, necessitating participants to be within the age range of 19 to 65 years, of female gender, and demonstrate a willingness to engage in the study. Consequently, this framework led to the exclusion of several demographic groups. Specifically, males and

individuals aged below 19 years or above 65 years were not eligible for participation in this research. This delineation of participant criteria ensured a focused and relevant sample population pertinent to the study's objectives centered on understanding fibromyalgia in the specified demographic.

Statistical Analysis

IBM Statistical Package for Social Sciences (SPSS) program Windows version 21.0 was used to evaluate the data obtained as a result of the research. Descriptive statistics for continuous variables in the study, such as mean, standard deviation, minimum, and maximum values, are expressed as numbers and percentages for categorical variables. The independent t-test was used to compare independent groups, and the One-way ANOVA test was used to compare the means of two or more groups. Pearson correlation coefficients were calculated to determine the relationship between variables. The chi-square test was used to determine the relationship between categorical variables. The statistical significance level was taken as $p<0.05$ in the calculations.

Results

This part of the study includes the patients' data and analyses. Findings regarding the general characteristics and health status of the patients are given in Table 1. The mean age of the patients participating in the study was 33.7±6.4 years. On average, the patients had been diagnosed with Fibromyalgia Syndrome (FMS) for 19.3±13.1 months and had been receiving treatment for 17.0±9.4 months. Regarding educational status, 22% of the patients had no formal education, 2% were literate without formal education, 29% had completed primary education, 7% had finished secondary school, 17% were high school graduates, and 23% had attained a university degree. Occupational distribution was such that 72% of the patients were homemakers, 25% were civil servants, and 3% were manual laborers. A family history of FMS was reported by 7% of the participants, with the highest prevalence of consanguinity observed in their mothers, accounting for 5% of the cases. It was observed that 4% of the participants had a BMI <18.50 kg/m², 29% had a BMI 20.00–24.99 kg/m², 59% had a BMI 25.00–29.99 kg/m² and 8% had a BMI 30.00–39.99 kg/m².

The anthropometric measurements of the participants are given in Table 2. It was observed that the mean height of the participants was 161.6±4.4, the mean body weight was 67.3±7.8, and the mean BMI was 25.8±3.1.

The FMS symptoms seen in the participants are shown in Table 3. According to these data, 93% of FMS patients had fatigue and muscle pain, and 91% had sleep disorders.

The participants' food preferences outside the home are shown in Table 4. It has been observed that 80% of the individuals prefer kebab types while eating outside the house, 78% prefer pita/lahmacun/flatbread, and 19% prefer fast food.

Table 1. *General characteristics and health conditions of the patients*

	$\bar{X}$ ± SD	Min- Max
Age (year)	33.7±6.4	21-46
Time to be diagnosed with FMS (months)	7.5-6.2	1-120
Treatment duration (months)	17.0-9.4	0-120
Level of education	**n**	**%**
Illiterate	22	22.0
Literate	2	2.0
Primary school	29	29.0
Middle School	7	7.0
High school	17	17.0
University	23	23.0
Occupation Status		
Housewife	72	72
Officer	25	25
Employee	3	3
Presence of FMS in the family		
Yes	7	7
No	93	93
Kinship Level		
Mother	5	5
Sibling	2	2
Body Mass Index (kg/m²)		
<18.50	4	4
18.50-24.99	29	29
25.00-29.99	59	59
30.00-39.99	8	8
>40.00	0	0
Total	100	100

Table 2. *Anthropometric measurements of the participants*

	$\bar{X}$	SD	Min	Max
Height (cm)	161.6	4.4	148.0	170.0
Weight (kg)	67.3	7.8	46.0	94.0
Body Mass Index (kg/m²)	25.8	3.1	18.0	36.7

Table 3. *Disease symptoms in individuals*

Symptom Sign	Yes		No		Total	
	n	%	n	%	n	%
Numbness and tingling in hands and feet	67	67	33	33	100	100
Intestinal complaints (such as gas, constipation, diarrhea)	46	46	54	54	100	100
Tiredness	93	93	7	7	100	100
Morning stiffness	44	44	56	56	100	100
Sleeping disorder	91	91	9	9	100	100
Muscle pains	93	93	7	7	100	100
Anxiety	6	6	4	4	100	100
Depression	29	29	71	71	100	100

Table 4. *Food preferences of the participants outside the home*

Type of food consumed outside the home	Yes		No		Total	
	n	%	n	%	n	%
Fast food (hamburger, pizza, bakedpotato, etc.)	19	19	81	81	100	100
Pita/lahmacun/pancake	78	78	22	22	100	100
Types of kebab	80	80	20	20	100	100
Grill types	27	27	73	73	100	100
Types of frying	1	1	99	99	100	100
Juicy home cooking (with meat)	2	2	98	98	100	100
Juicy home cooking (without meat)	0	0	100	100	100	100
Salad varieties	3	3	97	97	100	100

Table 5. *The relationship between the education level and occupation of the participants and their food preferences outside the home*

	Fast food	Piza/ lahmacun/ Pancake	Kebap	Grilled	Roast	Home-cooked meals (with meat)	Home-cooked meals (without meat)	Salad
	p	p	p	p	p	p	p	p
Education status	<0.001	0.304	0.301	0.060	0.641	0.204	-	0.262
Job	<0.001	0.016	0.602	0.021	0.220	0.672	-	0.010

Chi-square Test; p<0.05

Table 6. *The relationship between fibromyalgia symptoms and food preferences outside the home*

	Fast food	Piza/ lahmacun/ Pancake	Kebap	Grilled	Roast	Home-cooked meals (withmeat)	Home-cooked meals (withoutmeat)	Salad
	p	p	p	p	p	p	p	p
Numbness and tingling inhands and feet	0.139	0.007	0.560	0.602	0.481	0.316	-	0.990
Intestinal complaints (such as gas, constipation, diarrhea)	0.705	0.163	0.160	0.521	0.276	0.122	-	0.466
Tiredness	0.503	0.663	0.695	0.923	0.783	0.695	-	0.629
Morning stiffness	0.485	0.036	0.920	0.611	0.257	0.107	-	0.422
Sleeping disorder	0.796	0.987	0.055	0.735	0.752	0.653	-	0.580
Muscle pains	0.321	0.499	0.061	0.025	0.798	0.717	-	0.044
Anxiety	0.881	0.489	0.833	0.719	<0.001	0.718	-	0.043
Depression	0.774	0.389	0.321	0.010	0.116	0.509	-	0.144

Chi-square Test; p<0.05

The relationship between the education level and occupation of the participants and their food preferences outside the home is shown in Table 5. It was observed that there was a significant relationship between the education level of the participants and fast food consumption. In addition, it was observed that there was a significant relationship between the professions of the participants and fast food, grill, and salad.

Information on the relationship between the participants' fibromyalgia symptoms and their food preferences outside the home is shown in Table 6. When the relationship between fibromyalgia disease symptoms and the type of food preferred when eating outside the house was examined, a significant relationship was observed between numbness in the hands and feet and consumption of pita bread/lahmacun/pancake. In addition, it was observed that there was a significant relationship between morning stiffness and consumption of pita/lahmacun/pancake, muscle aches and pita/lahmacun and salad consumption, anxiety and frying consumption, depression, and grill consumption.

The findings regarding the relationship between the body mass indexes of the participants and the symptoms of fibromyalgia disease are shown in Table 7. The relationship between fibromyalgia disease symptoms and BMI was found to be significantly correlated with fibromyalgia symptoms such as fatigue, anxiety, and depression.

Table 7. *The relationship between the participants' body mass indexes and fibromyalgia disease symptoms*

	Body mass index
	p
Numbness and tingling in hands and feet	0.234
Intestinal complaints (such as gas, constipation, diarrhea)	0.28
Tiredness	0.011
Morning stiffness	0.388
Sleeping disorder	0.079
Muscle pains	0.385
Anxiety	<0.001
Depression	<0.001

Independent t Test; p<0.05

Discussion

This investigation assessed the nutritional status and dietary habits of fibromyalgia syndrome (FMS) patients attending the Physical Therapy and Rheumatology Outpatient Clinics at Van Training and Research Hospital in April 2018. One hundred female participants were enrolled following informed consent.

Demographic analysis revealed a mean age of 33.7±6.4 years, predominantly female, deviating slightly from the traditional demographic associated with FMS, suggesting an evolving age-related prevalence pattern. This observation aligns with recent epidemiological studies indicating a downward shift in age distribution among FMS patients[9,10]. Gender predominance remains consistent with established trends in FMS epidemiology, as recent literature reports a higher incidence in females[11,12].

Educational attainment among participants varied widely, reflecting FMS's indiscriminate impact across educational levels, a finding corroborated by recent scholarly research[13,14].

An emerging focus in FMS research is the correlation between occupational engagement and the syndrome's prevalence. Most of our study cohort were homemakers, paralleling findings from other studies that noted increased FMS cases in sectors with labor force growth[15]. Furthermore, the nexus between FMS and psychological morbidities such as depression and anxiety was evident, with 29% of our cohort diagnosed with depression. This is consistent with findings from Malik et al., who reported a 60% depression rate among FMS patients[16], and other research underscoring the frequent medical consultations by FMS patients with concurrent depression[17].

Symptomatic manifestations of FMS, including neuropathic discomfort, gastrointestinal disturbances, fatigue, sleep irregularities, musculoskeletal pain, and psychological distress, were prevalent in our study cohort, particularly fatigue, myalgia, and sleep disruptions. This aligns with literature documenting the ubiquity and seasonal exacerbation of these symptoms[18,19].

Our analysis also supports recent research trends linking elevated BMI with increased FMS prevalence and symptom intensity[20,21]. The intricate interplay among obesity, depressive states, and anxiety within the FMS patient population mirrors recent scholarly discourse[22,23].

Conclusion

As a result, in this study, it was determined that the obesity rate is high in fibromyalgia patients, and it is observed more frequently in homemakers. The most common symptoms encountered by the participants were fatigue, muscle aches, and sleep disturbances. It was observed that the BMI of the participants was significantly correlated with fatigue, anxiety, and depression, which are fibromyalgia symptoms. In line with these results, it is known that obesity is associated with fibromyalgia symptoms, and medical nutrition therapy compatible with obesity is recommended.

In the treatment of fibromyalgia syndrome, it was concluded that patients should be directed to a dietitian after diagnosis to reduce symptoms and increase their quality of life. Body mass index should also be taken into account while evaluating nutritional status.

Ethical Approval

For this study, "Ethics Committee Approval" no: 92, dated 12.03.2018, was received from Okan University Clinical Research Ethics Committee.

Financial Resource

No institution or company supported this research.

Conflict of Interest

There is no conflict of interest with any institution or person in the study.

Author Contributions

Idea/Concept: HT; Design: HT; Supervision/Consultancy: MT; Data Collection/Processing: HT; Analysis/Interpretation: HT, MT; Literature Review: HT; Writing the Article: HT; Critical Review: MT.

References

1. Giorgi V, Sirotti S, Romano ME, Marotto D, Ablin JN, Salaffi F, Sarzi-Puttini P. Fibromyalgia: one year in review 2022. Clin Exp Rheumatol. 2022;40(6):1065–1072.
2. Bair MJ, Krebs EE. Fibromyalgia. Ann Intern Med. 2020;172(5): ITC33-ITC48.
3. Sarzi-Puttini P, Giorgi V, Marotto D, Atzeni F. Fibromyalgia: an update on clinical characteristics, aetiopathogenesis and treatment. Nat Rev Rheumatol. 2020;16(11):645–660.
4. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RL, Mease PJ, Russell AS, Russell IJ, Walitt B. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum. 2016;46(3):319–329.
5. Marques AP, Santo ASE, Berssaneti AA, Matsutani LA, Yuan SLK. Prevalence of fibromyalgia: literature review update. Rev Bras Reumatol Engl Ed. 2017;57(4):356–363.
6. Assavarittirong C, Samborski W, Grygiel-Górniak B. Oxidative Stress in Fibromyalgia: From Pathology to Treatment. Oxid Med Cell Longev. 2022. 5:2022:1582432.
7. Rus A, Robles-Fernandez I, Martinez-Gonzalez LJ, Carmona R, Alvarez-Cubero MJ. Influence of Oxidative Stress-Related Genes on Susceptibility to Fibromyalgia. Nurs Res. 2021;70(1):44–50.
8. Lowry E, Marley J, McVeigh JG, McSorley E, Allsopp P, Kerr D. Dietary Interventions in the Management of Fibromyalgia: A Systematic Review and Best-Evidence Synthesis. Nutrients. 2020;12(9):2664.
9. Miller A, Johnson B, Lee C. Latest Study on Age Trends in Fibromyalgia Syndrome (FMS). J Pain and Chronic Conditions. 2022;68(1):102–117.
10. Singh D, Patel E, Thompson F. Recent Research on Younger Demographics in Fibromyalgia Syndrome (FMS). Fibromyalgia Focus. 2021;60(2):88–104.
11. Green G, Hernandez H, Kim I. Contemporary Analysis of Gender Prevalence in Fibromyalgia Syndrome (FMS). Chronic Illness Review. 2023;77(3):143–158.
12. O'Connor J, Li K, Martinez L. New Findings on Female Dominance in Fibromyalgia Syndrome (FMS) Cases. Women's Health and Chronic Pain. 2022;82(4):199–215.
13. Zhang M, Tanaka N, Gupta O. Study on Educational Backgrounds Among Fibromyalgia Syndrome (FMS) Patients. Educational Trends in Health. 2021;56(5):230–244.
14. Russo P, Clark Q, Nguyen R. Recent Insights into Education Levels in Fibromyalgia Syndrome (FMS). Socioeconomic Aspects of Health. 2023;101(6):275–290.
15. Kapoor S, Chen T, Williams U. Analysis of Occupational Status and Its Correlation with Fibromyalgia Syndrome (FMS). Occupational Health Journal. 2022;89(7):310–325.
16. Malik V, Davis W, Thompson X. Current Research on Psychological Health in Fibromyalgia Syndrome (FMS). Mental Health and Chronic Disease. 2023;103(8):156–172.
17. Johnson Y, Patel Z, Lee A. Latest Findings on Depression and Anxiety in Fibromyalgia Syndrome (FMS). Psychological Aspects of Fibromyalgia. 2021;65(9):118–134.
18. Smith B, Garcia C, Lopez D. Updated Review of Fibromyalgia Syndrome (FMS) Symptomatology. Journal of Chronic Pain. 2022;74(10):167–183.
19. Hernandez E, Kim F, Martinez G. Research on Environmental and Psychological Triggers in Fibromyalgia Syndrome (FMS). Environmental Health Perspectives. 2021;59(11):249–265.
20. Clark H, Nguyen I, Patel J. Contemporary Study on Body Mass Index (BMI) and Fibromyalgia Syndrome (FMS). Nutritional Research in Chronic Conditions. 2023;78(12):200–216.
21. Gomez K, Lee L, O'Connor M. Recent Research on Obesity Prevalence in Fibromyalgia Syndrome (FMS). Obesity and Chronic Illness. 2022;66(13):190–207.
22. Davis N, Thompson O, Patel P. Latest Findings on Obesity and Depression in Fibromyalgia Syndrome (FMS). Journal of Obesity and Mental Health. 2023;85(14):120–136.
23. Williams Q, Russo R, Zhang S. Current Study on Obesity, Depression, and Anxiety in Fibromyalgia Syndrome (FMS). Comprehensive Health Research. 2021;72(15):257–273.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Neutrophil-Lymphocyte Ratio in Septic Arthritis Diagnosis and Treatment Follow-Up

Septik Artritin Tanı ve Tedavi Takibinde Nötrofil-Lenfosit Oranı

Rifat Sahin[1], Mehmet Sabri Balik[1]

[1]*Department of Orthopedics and Traumatology, Recep Tayyip Erdogan University, Rize, Türkiye*

ABSTRACT

Aim: *This study aimed to determine the availability of neutrophil-to-lymphocyte ratio (NLR) in diagnosis and treatment follow-up by determining the changing values when septic arthritis (SA) is diagnosed and during treatment.*

Material and Method: *This retrospective study is based on examining the laboratory results of 44 adult patients with a diagnosis of SA. Laboratory values, white blood cell count (WBC), C-reactive protein (CRP), and NLR of the patients on days 0, 5, 10, and 14 and the results of the joint fluid analysis were evaluated.*

Results: *The mean number of cells in the joint fluid of the patients was 46 thousand, and the mean PMNL rate was 89.4%. Microorganisms were seen in gram staining of joint puncture fluid of only four patients (9.1%). The number of patients with growth in joint fluid culture was only 11 (25%). The mean values for days 0, 5, 10, and 14 were, respectively, 135.2, 88.1, 47.3, and 22.2 for CRP; 9.94, 7.86, 7.42, and 7.44 for WBC; 4.9, 3.8, 3.0 and 2.4 for NLR.*

Conclusion: *NLR may serve as a valuable biomarker for diagnosing and monitoring treatment in SA, particularly given the low prevalence of microorganisms in gram stains and joint fluid cultures and the variability in cell counts in joint fluid samples. In patients diagnosed with SA, the mean NLR value is 4.9 and consistently decreases during treatment. Within two weeks of initiating treatment, NLR typically decreases by approximately half. This biomarker can aid in diagnosing and ongoing managing SA, offering a cost-effective and readily available indicator that should be routinely considered.*

Key words: *arthritis; septic; neutrophils; lymphocytes; biomarkers*

ÖZET

Amaç: *Bu çalışmada nötrofil-lenfosit oranının (NLR), septik artrit (SA) tanısı konulduğundaki ve tedavi sürecindeki değişen değerleri belirlenerek tanı ve tedavi takibindeki kullanılabilirliğini saptamak amaçlanmıştır.*

Materyal ve Metot: *Bu retrospektif çalışma, SA tanısı ile tedavi edilen 44 erişkin hastanın laboratuvar sonuçlarının incelenmesine dayanmaktadır. Hastaların 0., 5., 10., 14. günlerdeki laboratuvar değerleri (WBC, CRP, NLR) ve eklem sıvısı analizinin sonuçları değerlendirildi.*

Bulgular: *Hastaların eklem sıvısındaki ortalama hücre sayısı 46 bin, ortalama PMNL oranı %89,4 idi. Sadece dört hastanın (%9,1) eklem ponksiyon sıvısının gram boyanmasında mikroorganizma görüldü. Eklem sıvısı kültüründe üreme görülen hasta sayısı sadece 11 idi (%25); 0., 5., 10. ve 14. günler için ortalama değerler CRP için sırasıyla 135,2, 88,1, 47,3 ve 22,2; WBC için 9,94, 7,86, 7,42 ve 7,44; NLR için 4,9, 3,8, 3,0 ve 2,4 idi.*

Sonuç: *Septik artritte gram boyama ve eklem sıvı kültüründe mikroorganizma görülme oranının oldukça düşük olması, eklem sıvısındaki hücre sayısının her zaman net fikir vermemesi nedeniyle tanı ve tedaviye yanıtı değerlendirmede biyobelirteç olarak NLR de yol gösterici olabilir. Septik artrit tanısı alan hastalarda ortalama NLR değeri 4,9 olup tedavi süresince düzenli olarak azalmaktadır. NLR, tedavinin 2. haftasında yaklaşık yarı değerine inmektedir. Bu biyobelirteç SA'nın tanı ve takibinde kullanılabilir. Ucuz ve kolay erişilebilir bir gösterge olduğu için NLR değeri her zaman dikkate alınmalıdır.*

Anahtar kelimeler: *artrit; septik; nötrofil; lenfosit; biyobelirteç*

İletişim/Contact: *Rifat Sahin, Department of Orthopedics and Traumatology, Recep Tayyip Erdogan University, Rize, Türkiye* • ***Tel:*** *0537 392 06 94* • ***E-mail:*** *drrifatsahin@hotmail.com* • ***Geliş/Received:23.01.2023*** • ***Kabul/Accepted:*** *25.03.2024*

ORCID: *Rıfat Şahin: 0000-0002-0609-5069* • *Mehmet Sabri Balık: 0000-0001-9729-3927*

Introduction

Acute bacterial arthritis or septic arthritis (SA) is an orthopedic emergency. Bacterial replication and subsequent inflammatory processes develop in the joint. This may cause severe deterioration in the joint and cause mortality as a result of sepsis. Therefore, the diagnosis and appropriate treatment of the infected joint is critical to limit the morbidity and mortality associated with these infections.

The incidence of SA is estimated to be about 2 to 10 cases per 100,000 per year[1]. Patients with a history of prosthetic joint replacement, rheumatoid arthritis, systemic lupus erythematosus, gouty arthropathy, diabetes mellitus, and immunosuppressive drug use are at higher risk of developing septic arthritis[2].

Early use of antibiotics directed against the causative pathogen, surgical irrigation of the joint, and debridement, if necessary, are essential in treating SA. The treatment process of these patients lasts for weeks. Common inflammation markers such as white blood cell count (WBC), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) for diagnosis and evaluation of of these infections have poor discriminatory capacity between infectious and noninfectious pathologies[3,4]. Although new markers such as procalcitonin and adrenomedullin have been introduced, the use of these markers has been limited due to cost, accessibility, and appropriate validation problems[4]. For these reasons, the search for inexpensive and reliable markers to predict SA and evaluate the response to treatment persists.

In recent years, studies have been conducted on inflammatory markers obtained from complete blood count (CBC) for early diagnosis of infection and evaluation of response to treatment[5–7]. Markers such as neutrophil-lymphocyte ratio (NLR), mean platelet volume (MPV), and calculation of platelet-lymphocyte ratio (PLR) were evaluated in different disease groups[8]. Since a limited number of studies use these markers in the treatment follow-up of adult SA, this study aimed to determine the use of NLR in diagnosing and treating SA, which requires urgent and long-term treatment.

Materials and Methods

This retrospective study examines the laboratory results of 44 patients with a diagnosis of SA who were treated and followed up in our hospital's orthopedics and traumatology clinic between January 2018 and November 2021 and who met the inclusion criteria.

The diagnosis of SA was made according to the number and content of cells in the joint puncture after the causative microorganism was isolated from the joint fluid or after the physical examination revealed signs of infection such as increased temperature, redness, swelling, and limitation of movement in the joint. Elevated CRP values in the blood and more than 20 thousand cells in the joint fluid or polymorphonuclear leukocytes (PMNL) ratios above 80% were used to guide the diagnosis.

Inclusion criteria for the study: Patients over 18 years of age who underwent joint puncture by us and were diagnosed with SA and underwent intra-articular arthroscopic washing, whom we followed up for at least 14 days.

Exclusion criteria: Patients under 18 years of age, patients with multiple joint involvements, undergoing open surgery, a history of the rheumatological disease, immune compromisation, SA, prosthetic joint replacement, bleeding diathesis, history of previous granulomatous disease and malignancy, requiring intensive care, and those who were cachectic or morbidly obese.

The medical history of all patients included in the study, their eligibility for inclusion, and the evidence for the diagnosis of SA were reviewed. Age, gender, and laboratory values (WBC, CRP, NLR) of the patients on days 0, 5, 10, and 14 were recorded.

The patients included in the study underwent arthroscopic intervention. Joint irrigation and debridement, when necessary, were routinely performed during surgery. Empirical intravenous antibiotic treatment of all patients postoperatively was started after consultation with infectious diseases. Antibiotherapy was adjusted according to the culture result, if necessary. Intravenous antibiotherapy was continued until the inflammatory markers approached normal and the patients were clinically relieved (minimum two weeks). In contrast, outpatient follow-up and treatment with oral antibiotics were continued.

This retrospective study was conducted under the principles stated in the Declaration of Helsinki. The search for archival material and research permission was obtained from the hospital administration and approved by the local ethics committee (approval number: 2022/45).

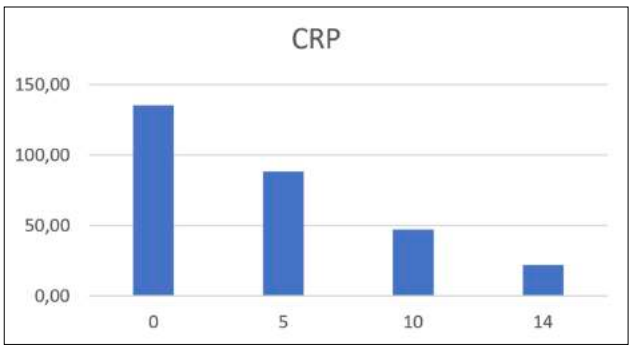

Figure 1. *Change of mean CRP value on days 0, 5, 10, and 14 (CRP: C-reactive protein).*

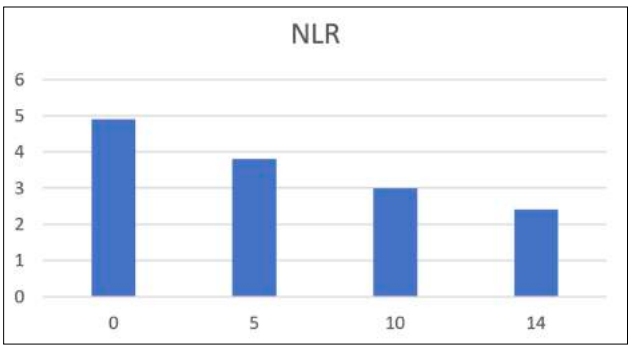

Figure 2. *Change of mean NLR value on days 0, 5, 10, and 14 (NLR: Neutrophil-to-lymphocyte ratio).*

Statistical method: The dataset was preprocessed (outlier, missing observation, normal distribution assumption). The descriptive statistics of the normally distributed continuous variables are given as X ± SD, the non-normally distributed continuous variables are given as median and min-max values, and the categorical variables (qualitative) are given as percentages and ratios. Comparisons were made between the normally distributed continuous variables and the groups using parametric methods. Statistical significance was accepted as $p < 0.05$.

Results

The mean age of 44 patients was 67.8 (range 40–91); 22 of them were male (50%) and 22 were female (50%). The involved joint in all cases was the knee, except for one in which the hip joint was affected.

The mean number of cells in the joint fluid of the patients was 46 thousand, and the mean PMNL rate was 89.4%. Microorganisms were seen in gram staining of joint puncture fluid of only four patients (9.1%), and these were gram (+) cocci. The number of patients with growth in joint fluid culture was only 11 (25%).

The mean values were calculated for 0, 5, 10, and 14 days when SA was diagnosed and during treatment (Table 1). Respectively, 135.2, 88.1, 47.3, and 22.2 for CRP (Fig. 1); 9.94, 7.86, 7.42 and 7.44 for WBC; 4.9, 3.8, 3.0 and 2.4 for NLR (Fig. 2).

The change in NLR value was compared according to the days, and p-values were calculated. Statistically, there was no significant decrease in the NLR value on the 5th day. Still, the p-value was <0.001 on the 10th and 14th days compared to the preoperative day. The comparison of the NLR value between itself according to the days is indicated below.

NLR (0) – NLR (5): p=0.098

NLR (0) – NLR (10): p<0.001

NLR (0) – NLR (14): p<0.001

NLR (5) – NLR (10): p=0.077

NLR (5) – NLR (14): p<0.001

NLR (10) – NLR (14): p=0.098

Discussion

In this study, in which septic arthritis diagnosis and response to treatment (we routinely prefer arthroscopic treatment as it is as effective as traditional open approaches, has a shorter hospital stay, additional benefits in postoperative wound healing, and offers better results than open surgery in postoperative joint range of motion[2,9]) were evaluated, the NLR value, which is an easily accessible and inexpensive biomarker, was calculated. The mean NLR value of patients diagnosed with septic arthritis was 4.9. The NLR value calculated as an alternative to the CRP value, primarily used in response to septic arthritis treatment, was found to be 3.8

Table 1. *Changes in CRP, WBC, and NLR values in the diagnosis of adult septic arthritis and during the treatment period*

PARAMETERS	Day 0	Day 5	Day 10	Day 14
CRP (0-5)	135.2	88.1	47.3	22.2
WBC (4-10)	9.94	7.86	7.42	7.44
NLR	4.9	3.8	3.0	2.4

CRP: C-reactive protein; **WBC:** White blood cell count; **NLR:** Neutrophil-to-lymphocyte ratio.

on the 5th day, 3.0 on the 10th day, and 2.4 on the 14th day of treatment. The NLR value decreased at similar rates to CRP in treating adult septic arthritis.

Bacterial isolation from synovial fluid obtained by joint puncture is the gold standard in diagnosing SA[10]. However, false-negative culture results may be seen due to antibiotic use before joint puncture[11] and false-positive results due to contamination[12,13]. In their prospective multicenter study, Gupta et al.[14] found growth in synovial fluid in only 57% of 82 patients diagnosed with SA. When they compared these patients with those lacking growth in the joint fluid, they reported that the groups' mortality and morbidity were similar. The fact that only 25% of the patients in our study had growth in the joint fluid culture supports the low sensitivity of joint fluid culture in diagnosing septic arthritis.

Although growth in blood culture is helpful in the diagnosis, Weston et al.[15] obtained a positive blood culture in only 24% of the 242 patients in their study. This result supports the idea that a negative blood culture cannot rule out infection. Therefore, additional objective marker inclusion in the diagnosis of septic arthritis will significantly benefit clinical practice. We do not routinely take blood cultures from patients who do not show signs of systemic infection.

A meta-analysis of 14 studies on SA evaluated 6242 patients[16]. They found joint pain (85%), joint redness (78%), an increase in joint temperature (57%), sweating (27%), and joint stiffness (19%). The same study showed that the probability of septic arthritis was low in patients with a leukocyte count below 25 thousand in the joint fluid, which increased significantly in those above 50 thousand, and it was specific for septic arthritis[2]. They also showed that the probability of SA was increased dramatically in those with a PMNL rate greater than 90%. The mean WBC count in the joint fluid of the patients with SA (43 thousand) and the rate of PMNL in the joint (89.4%) in this study are similar to those reported in this meta-analysis.

It is known that an increase in WBC in the blood may be associated with infection. Still, leukopenia can also be seen in infective conditions[17]. White blood cell count level is also frequently affected by non-infective conditions such as steroid use[18]. Many studies have shown that WBC has a low diagnostic value in the diagnosis of infection[18–20]. Our study determined that although some patients had high WBC values, the mean WBC value was within the normal reference range from the first day to the 14th day. However, the mean WBC value decreased with treatment. Although CRP has a high sensitivity in the diagnosis of infection, it is far from being reliable in the diagnosis and follow-up of infection since it increases in inflammatory conditions such as surgery and trauma[21–23], in patients with malignancy[24], and even in obesity[25].

In the differential diagnosis of septic arthritis, clinicians should also consider diseases such as transient synovitis, rheumatoid arthritis, reactive arthritis, abscess, avascular necrosis, cellulitis, crystal-induced arthropathies such as gout, Lyme disease, osteomyelitis, and malignancy[26]. A combination of biomarkers may help diagnose SA since physical examination findings may differ from patient to patient[16], blood results are affected by many clinical conditions [17,18,21–25,] and false negative culture may be present[11]. Manohar et al.[4] showed that high NLR has a similar diagnostic value to blood culture positivity in diagnosing systemic infection. We also evaluated NLR as a measure of systemic inflammation in the diagnosis and follow-up of SA, where early diagnosis and treatment are very important.

None of the readily available and inexpensive biomarkers, such as ESR, CRP, and WBC, have a cut-off value for septic arthritis. There is no acceptable sensitivity or diagnostic accuracy of the peripheral WBC count for diagnosing septic arthritis. Multiple studies demonstrated acceptable sensitivity for ESR of >30 mm/hour, but the specificities were poor. There is no cut-off for ESR or CRP yet for septic arthritis. Tumor necrosis factor and various cytokines, including interleukin-6 and interleukin-β, were generally specific with poor sensitivity. Procalcitonin levels are typically elevated because the etiology of septic arthritis is usually systemic[27]. Neutrophil-to-lymphocyte ratio is an inexpensive and readily available indicator of systemic inflammation based on complete blood count values. In general, the number of neutrophils in the blood increases with the progression of the inflammatory state. As the neutrophil count increases, the lymphocyte count decreases. As a result, NLR increases, which is considered an indicator of systemic inflammation[28]. But this is not always the case. In some cases, such as cachexia, false negativity may occur because the neutrophil count is not increased. The lymphocyte count reflects the patient's immune status and generally decreases as the inflammatory disease progresses[29]. Recent studies have shown that NLR is more reliable on patient survival than neutrophil or lymphocyte count alone[30].

In a study to determine the normal value of NLR, the mean NLR value in healthy adults was reported as 1.65 (0.78–3.53)[31]. Gurol et al.[32], in their study on the NLR value, showed that the cut-off value for sepsis was 5. In our research, while the mean NLR value of the patients on the first day was 4.9, it decreased to 3.8, 3.0, and 2.4 on the 5 th, 10 th, and 14th days after treatment, respectively. This 3-fold increase compared to the normal value on the first day may be significant in diagnosing SA. In addition, the decrease in NLR over time in patients who underwent surgical treatment and antibiotic therapy indicates that it may be a sign of response to treatment. While NLR decreased during treatment, there was also a regression in the clinic and symptoms. An improvement was observed in the patient's general condition and systemic findings, often starting from the second day. However, it was generally observed after the fifth day that patients mobilized without pain and felt that they were beginning to recover. This was parallel to the significant decrease in NLR.

Study Limitations

A limitation of this study was that it was retrospective and single-centered. Studies with a more extensive series, prospective, and comparing biomarkers will be more useful. It would be beneficial if other biomarkers, such as PLR MPV, were compared.

Conclusion

Due to the low incidence of microorganisms in gram staining in the diagnosis of SA, the need for time for reproduction in culture, and the number of cells in the joint fluid does not always give a clear idea; it may be useful to evaluate biomarkers for diagnosis and treatment in SA, which requires urgent diagnosis and treatment. NLR, calculated as a simple ratio between the neutrophil and lymphocyte counts measured in peripheral blood, is a biomarker that reflects the balance between two aspects of the immune system: acute and chronic inflammation (as indicated by the neutrophil count) and adaptive immunity (lymphocyte count). Neutrophil-to-lymphocyte ratio is not a new biomarker. It has been previously evaluated in many conditions, such as infection, malignancy, rheumatological disease, and appendicitis, and it has been shown that it can be used as a prognostic factor[4,8,33,34]. It is one of the few studies that show its importance in adult septic arthritis.

In patients diagnosed with septic arthritis in adults, the average NLR value is 4.9 and decreases regularly during the treatment process. After approximately two weeks of treatment, this rate decreases to half its value. Based on the results of this study, NLR is an inflammatory marker that can be used in the diagnosis and follow-up of SA treatment. Neutrophil-to-lymphocyte ratio value should always be considered because it is a cheap and easily accessible indicator.

References

1. Clerc O, Prod'hom G, Greub G, Zanetti G, Senn L. Adult native septic arthritis: a review of 10 years of experience and lessons for empirical antibiotic therapy. J Antimicrob Chemother. 2011;66(5):1168–73.
2. Elsissy JG, Liu JN, Wilton PJ, Nwachuku I, Gowd AK, Amin NH. Bacterial Septic Arthritis of the Adult Native Knee Joint: A Review. JBJS Rev,. 2020;8(1):e0059.
3. Wyllie DH, Bowler IC, Peto TE. Bacteraemia prediction in emergency medical admissions: role of C reactive protein. J Clin Pathol. 2005;58(4):352–6.
4. Manohar V, Prasad SB, Raj S, Sreekrishnan TP, Gireesh Kumar KP. The Eminence of Neutrophil-lymphocyte Count Ratio in Predicting Bacteremia for Community-acquired Infections at an Emergency Medicine Department in a Tertiary Care Setting. J Emerg Trauma Shock. 2018;11(4):271–5.
5. Hwang SY, Shin TG, Jo IJ, et al. Neutrophil-to-lymphocyte ratio as a prognostic marker in critically ill septic patients. Am J Emerg Med. 2017;35(2):234–9.
6. Prozan L, Shusterman E, Ablin J, et al. Prognostic value of neutrophil-to-lymphocyte ratio in COVID-19 compared with Influenza and respiratory syncytial virus infection. Sci Rep. 2021;2;11(1):21519.
7. Stojkovic Lalosevic M, Pavlovic Markovic A, Stankovic S, et al. Combined Diagnostic Efficacy of Neutrophil-to-Lymphocyte Ratio (NLR) , Platelet-to-Lymphocyte Ratio (PLR) , and Mean Platelet Volume (MPV) as Biomarkers of Systemic Inflammation in the Diagnosis of Colorectal Cancer. Dis Markers. 2019;17;2019:6036979.
8. Sarı R, Karakurt Z, Ay M, et al. Neutrophil to lymphocyte ratio as a predictor of treatment response and mortality in septic shock patients in the intensive care unit. Turk J Med Sci. 2019;24;49(5):1336–49.
9. Johns BP, Loewenthal MR, Dewar DC. Open Compared with Arthroscopic Treatment of Acute Septic Arthritis of the Native Knee. J Bone Joint Surg Am. 2017;15;99(6):499–5.
10. Fowler ML, Zhu C, Byrne K, et al. Pathogen or contaminant? Distinguishing true infection from synovial fluid culture contamination in patients with suspected septic arthritis. Infection. 2017;45(6):825–30.

11. Hindle P, Davidson E, Biant LC. Septic arthritis of the knee: the use and effect of antibiotics prior to diagnostic aspiration. Ann R Coll Surg Engl. 2012;94(5):351–5.
12. Setya D, Pandey P, Ranjan S, Kumar D, Das S. Recapping error: A case of false positive result due to minuscule contamination by re-closure of vacutainer. Indian J Pathol Microbiol. 2020;63(4):678–80.
13. Montgomery TL, Paavola M, Bruce EA, Botten JW, Crothers JW, Krementsov DN. Laboratory Worker Self-Contamination with Noninfectious SARS-CoV-2 DNA Can Result in False-Positive Reverse Transcriptase PCR-Based Surveillance Testing. J Clin Microbiol. 2021;18;59(7):e0072321.
14. Gupta MN, Sturrock RD, Field M. Prospective comparative study of patients with culture proven and high suspicion of adult onset septic arthritis. Ann Rheum Dis. 2003;62(4):327–31.
15. Weston VC, Jones AC, Bradbury N, Fawthrop F, Doherty M. Clinical features and outcome of septic arthritis in a single UK Health District 1982–1991. Ann Rheum Dis. 1999;58(4):214–9.
16. Margaretten ME, Kohlwes J, Moore D, Bent S. Does this adult patient have septic arthritis? JAMA. 2007;4;297(13):1478–88.
17. Kochanek M, Böll B, Hallek M, von Bergwelt-Baildon M. Neutropenie und Sepsis [Neutropenia and sepsis]. Internist (Berl) . 2013;54(9):1061–9.
18. Póvoa P, Coelho L, Almeida E, et al. Early identification of intensive care unit-acquired infections with daily monitoring of C-reactive protein: a prospective observational study. Crit Care. 2006;10(2):R63.
19. Peres Bota D, Mélot C, Lopes Ferreira F, Vincent JL. Infection Probability Score (IPS): A method to help assess the probability of infection in critically ill patients. Crit Care Med. 2003;31(11):2579–84.
20. Adnet F, Borron SW, Vicaut E, et al. Value of C-reactive protein in the detection of bacterial contamination at the time of presentation in drug-induced aspiration pneumonia. Chest. 1997;112(2):466–1.
21. Alper B, Erdogan B, Erdogan MÖ, Bozan K, Can M. Associations of Trauma Severity with Mean Platelet Volume and Levels of Systemic Inflammatory Markers (IL1β, IL6, TNFα, and CRP). Mediators Inflamm. 2016:9894716.
22. Du Clos TW. Function of C-reactive protein. Ann Med. 2000;32(4):274–8.
23. Muñoz JL, Alvarez MO, Cuquerella V, et al. Procalcitonin and C-reactive protein as early markers of anastomotic leak after laparoscopic colorectal surgery within an enhanced recovery after surgery (ERAS) program. Surg Endosc. 2018;32(9):4003–10.
24. Shen J, Hernandez D, McNeill LH, Chow WH, Zhao H. Associations of serum CRP levels with demographics, health behaviors, and risk of cancer among the Mexican American Mano A Mano Cohort. Cancer Epidemiol. 2019;60:1–7.
25. Paepegaey AC, Genser L, Bouillot JL, Oppert JM, Clément K, Poitou C. High levels of CRP in morbid obesity: the central role of adipose tissue and lessons for clinical practice before and after bariatric surgery. Surg Obes Relat Dis. 2015;11(1):148–54.
26. Long B, Koyfman A, Gottlieb M. Evaluation and Management of Septic Arthritis and its Mimics in the Emergency Department. West J Emerg Med. 2019;20(2):331–41.
27. Carpenter CR, Schuur JD, Everett WW, Pines JM. Evidence-based diagnostics: adult septic arthritis. Acad Emerg Med. 2011;18(8):781–96.
28. Imtiaz F, Shafique K, Mirza SS, Ayoob Z, Vart P, Rao S. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. Int Arch Med. 2012;26;5(1):2.
29. Huang Z, Fu Z, Huang W, Huang K. Prognostic value of neutrophil-to-lymphocyte ratio in sepsis: A meta-analysis. Am J Emerg Med. 2020;38(3):641–7.
30. Kumarasamy C, Sabarimurugan S, Madurantakam RM, et al. Prognostic significance of blood inflammatory biomarkers NLR, PLR, and LMR in cancer-A protocol for systematic review and meta-analysis. Medicine (Baltimore) . 2019;98(24):e14834.
31. Forget P, Khalifa C, Defour JP, Latinne D, Van Pel MC, De Kock M. What is the normal value of the neutrophil-to-lymphocyte ratio? BMC Res Notes. 2017;3;10(1):12.
32. Gürol G, Çiftci İH, Terizi HA, Atasoy AR, Ozbek A, Köroğlu M. Are there standardized cutoff values for neutrophil-lymphocyte ratios in bacteremia or sepsis? J Microbiol Biotechnol. 2015;25(4):521–5.
33. Erre GL, Paliogiannis P, Castagna F, et al. Meta-analysis of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio in rheumatoid arthritis. Eur J Clin Invest. 2019;49(1):e13037.
34. Diem S, Schmid S, Krapf M, et al. Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. Lung Cancer. 2017;111:176–81.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of Health Literacy and Health Perception in Individuals with Chronic Diseases

Kronik Hastalığı Olan Bireylerde Sağlık Okuryazarlık ve Sağlık Algısının Değerlendirilmesi

Hilal Kale Aktas[1], Recep Aktas[1], Okcan Basat[2]

[1]Gediz District Health Directorate, Kutahya; [2]Department of Family Medicine, Gaziosmanpasa Training and Research Hospital, University of Health Sciences, Istanbul, Türkiye

ABSTRACT

Aim: *Health literacy is essential for treatment adherence and significantly affects disease management. This study aims to assess the health literacy and perception levels of individuals with chronic diseases.*

Material and Method: *The study was a single-centered cross-sectional study. The study population included patients who applied to the Family Medicine Outpatient Clinic in The Training and Research Hospital. The study analyzed data from 360 patients, examining their socio-demographic information and health status using a questionnaire. The questionnaire was prepared using a face-to-face method. The participants' health literacy levels were assessed using a health literacy questionnaire, and their health perceptions were determined using a health perception questionnaire.*

Results: *Out of the 360 participants in the study, 56.9% were women. The mean health perception score was 47.13±15.47, and the mean health literacy score was 102.19±15.98. A positive correlation was found between individuals' health literacy levels and their level of care for their health. The study observed that individuals with high health literacy did not struggle to access and comprehend medical information. They could use health services promptly and effectively (p1<0.001, p2:0.005; respectively).*

Conclusion: *Research has demonstrated a positive and significant correlation between health literacy and understanding of health information among individuals who manage their health. The level of health literacy is determined by factors such as age, income level, and educational status.*

Keywords: *health literacy; chronic disease; family practice*

ÖZET

Amaç: *Sağlık okuryazarlığı, tedaviye uyumda önemli bir unsurdur ve hastalık yönetimi sürecini önemli ölçüde etkilemektedir. Bu çalışma, kronik hastalığı olan bireylerin sağlık okuryazarlığı ve algı düzeylerini değerlendirmeyi amaçlamaktadır.*

Materyal ve Metot: *Çalışma tek merkezli kesitsel bir çalışmadır. Çalışmanın evrenini Eğitim ve Araştırma Hastanesi Aile Hekimliği Polikliniğine başvuran hastalar oluşturmuştur. Çalışmada 360 hastadan elde edilen veriler analiz edilmiş, sosyo-demografik bilgileri ve sağlık durumları bir anket kullanılarak incelenmiştir. Anket yüz yüze görüşme yöntemi kullanılarak hazırlanmıştır. Katılımcıların sağlık okuryazarlığı düzeyleri sağlık okuryazarlığı anketi ile değerlendirilmiş ve sağlık algıları sağlık algısı anketi ile belirlenmiştir.*

Bulgular: *Çalışmaya katılan 360 kişinin %56,9'u kadındır. Ortalama sağlık algısı puanı 47,13±15,47'dir ve ortalama sağlık okuryazarlığı puanı 102,19±15,98'dir. Bireylerin sağlık okuryazarlığı düzeyleri ile sağlıklarını önemseme düzeyleri arasında pozitif bir ilişki bulunmuştur. Çalışmada sağlık okuryazarlığı yüksek olan bireylerin tıbbi bilgiye ulaşma ve anlama konusunda zorluk yaşamadıkları, sağlık hizmetlerini zamanında ve etkili bir şekilde kullanabildikleri saptanmıştır (sırasıyla p1<0,001, p2:0,005).*

Sonuç: *Bu araştırma, kendi sağlıklarını yöneten bireylerin sağlık okuryazarlığı düzeyi ile sağlık bilgilerini anlama düzeyi arasında pozitif ve anlamlı bir ilişki olduğunu ortaya koymuştur. Sağlık okuryazarlığı düzeyi yaş, gelir düzeyi ve eğitim durumu gibi faktörler tarafından belirlenmektedir.*

Anahtar kelimeler: *sağlık okuryazarlığı; kronik hastalık; aile hekimliği*

İletişim/Contact: *Hilal Kale Aktas, Gediz Provincial Health Directorate, Family Medicine Department, Kutahya, Türkiye* • ***Tel:*** *0505 605 45 45* • ***E-mail:*** *dr.hilalkale@gmail.com* • ***Geliş/Received:*** *30.01.2023* • ***Kabul/Accepted:*** *15.03.2024*

ORCID: *Hilal Kale Aktaş: 0000-0001-9812-8376* • *Recep Aktaş: 0000-0002-5576-6623* • *Okcan Başat: 0000-0002-5222-9136*

Introduction

Chronic illnesses stand as a prevalent cause of global mortality and morbidity, placing substantial strain on healthcare systems and public budgets[1,2]. Health literacy is vital to mitigating this burden, a key determinant in accessing healthcare services and fostering a healthy lifestyle. Its impact extends beyond individual well-being, influencing social productivity and contributing to the reduction of mortality and morbidity, consequently alleviating healthcare costs[3]-[5].

Health perception encapsulates individuals' well-being assessments, shaped by beliefs, attitudes, education, emotions, and environmental factors[6–8]. Integral to this is perceived health perception, the beliefs, attitudes, and actions individuals adopt to maintain their health[9]. Recognizing its fundamental role in overall health and well-being, sustaining healthy behaviors becomes paramount over time[10].

This study aims to explore the interplay between health literacy and the health perception of individuals grappling with chronic diseases.

Materials and Methods

This study was conducted between December 1, 2020, and February 1, 2021, at the Family Medicine Outpatient Clinic in The Training and Research Hospital. The study comprised 360 patients with chronic illnesses. Patients were provided with detailed information about the survey's objectives. After obtaining patients' consent, their health status was assessed through face-to-face interviews using a socio-demographic form designed by the researchers. The participants were administered the Health Literacy Scale and Health Perception Scale, and the results were recorded. The study was approved by the Clinical Research Ethics Committee of the Istanbul Gaziosmanpasa Training and Research Hospital under the Ministry of Health on 23.09.2020 (No. 159).

We utilized the simple random sampling method to determine the sample size for our study population. The study population encompassed 4800 individuals aged 18 and above, all of whom had applied to the Family Medicine Outpatient Clinic in the Training and Research Hospital for one year. To guarantee the representativeness of our sample, we used key parameters: q=0.5, d=0.05, and p=0.5. Based on these considerations, we established that a minimum of 358 individuals with chronic diseases should be included in our study. This meticulous approach ensures statistical reliability and strengthens the study's capacity to yield meaningful insights representative of the broader population.

The scales utilized in this study were developed based on the research conducted by Aras et al.[11] on the validity and reliability of the Turkish version of the Health Literacy Scale and by Kadioğlu et al.[12] on the validity and reliability of the Turkish version of the Health Perception Scale.

The Health Perception Scale is a five-point Likert-type scale developed by Diamond et al.[13] The scale comprises 15 items and four sub-factors, namely 'center of control' , 'self-awareness' , 'certainty' , and 'importance of health' . The scale includes six items with a positive attitude (1st, 5th, 9th, 10th, 11th, and 14th) and nine items with negative statements (2nd, 3rd, 4th, 6th, 7th, 8th, 12th, 13th, and 15th). 'strongly agree' is assigned a score of 5, 'agree' is assigned a score of 4, 'undecided' is assigned a score of 3, 'disagree' is assigned a score of 2, and 'strongly disagree' is assigned a score of 1. Negative statements are scored in reverse. The scoring system for statements is as follows: The scale ranges from a minimum score of 15 to a maximum score of 75.

The Health Literacy Scale is a 25-item Likert-type scale that was developed by Toci et al.[14] It consists of four subscales: 'Access to Information' (items 1–5), 'Understanding Information' (items 6–12), 'Appraising/Evaluating' (items 13–20), and 'Applying/Using' (items 21–25). The minimum score for the entire scale is 25, and the maximum score is 125. The scale items are answered by the participants on a Likert scale as 5:I have no difficulty at all, 4:I have little difficulty, 3:I have some difficulty, 2:I have a lot of difficulty, 1:I am unable to do it / I have no ability / impossible". The scale contains only positive items, and there are no reverse items. Low scores indicate inadequate, problematic, and weak health literacy status, while high scores indicate adequate and very good status. As the score increases, the individual's health literacy level also increases.

Licensed Statistical Package for Social Sciences SPSS for Windows, program version 22.0 (IBM, Türkiye), was used for statistical analysis. Shapiro-Wilk's test assessed whether parameters were suitable for normal distribution. Descriptive statistical methods were used, such as mean, standard deviation, and

frequency. The One-way ANOVA test was used to compare parameters that showed a normal distribution between more than two groups, and the Tukey HDS test was used to determine the group responsible for the difference.

The Kruskal-Wallis test and Dunn's test were used to determine the group responsible for the differences in the parameters that did not exhibit normal distribution among more than two groups. The Student t-test was used for comparisons between two groups for the parameters exhibiting normal distribution, and the Mann-Whitney U test was used for comparisons between two groups for the parameters not exhibiting normal distribution. Pearson's correlation analysis was used to examine the relationships between the parameters that were normally distributed, while Spearman's rho correlation analysis was used for those that were not. The Chi-Square test was used to compare qualitative data, and $p<0.05$ was considered statistically significant.

Results

Participants ranged from 27 to 83, with a mean age of 52.05±11.62. Among attendees, 56.9% were women, and 69.2% were married. Moreover, 72.8% of participants held high school or university degrees. Detailed socio-demographic data are presented in Table 1.

It has been observed that as participants age, they place greater importance on their health. There is a significant correlation between age and health ($p<0.05$). A negative correlation of 19.3% was observed between increasing participant age and their understanding of medical knowledge ($p<0.01$). A negative correlation of 13.3% ($p<0.05$) was noted between the participants' age and health literacy level.

A noteworthy observation is the low correlation between effective healthcare service utilization and understanding medical knowledge among individuals older than 65 ($p<0.05$). Details of the age-related correlations are summarized in Table 2.

Examining the influence of education on health literacy, individuals with university degrees exhibited significantly higher health literacy levels than those with secondary or high school education ($p1<0.01$, $p2<0.01$, respectively).

Individuals with higher incomes place greater importance on their health and utilize healthcare facilities more effectively than those with lower incomes ($p1<0.01$, $p2<0.01$, respectively). Moreover, individuals with higher incomes have greater access to medical knowledge and a better understanding of it than those with lower incomes, with statistically significant differences ($p1<0.01$, $p2<0.01$, respectively). The health literacy level of high-income groups is significantly higher than that of low-income groups ($p<0.01$). Table 3 presents the correlation between participants' income levels and the scales.

Research findings underscore that individuals possessing high levels of health literacy display adeptness in quickly accessing medical knowledge, interpreting medical information, utilizing health services

Table 1. *Socio-demographic data of participants*

		Min-Max	Mean ± SD
Age		27-83	52.05±11.62
		n	**%**
Age group	45 and younger	118	32.8
	46-54 age	90	25
	55-64 age	94	26.1
	65 and older	58	16.1
Gender	Female	205	56.9
	Male	155	43.1
Marital status	Married	249	69.2
	Unmarried	111	30.8
Education status	Illiterate	12	3.3
	Elementary	63	17.5
	Middle school	23	6.4
	High School	91	25.3
	University	171	47.5
Work experience	1-3 years	86	23.9
	3-5 years	38	10.6
	5-10 years	63	17.5
	10 years and over	173	48.1
Income status	Low income	56	15.6
	Middle income	77	21.4
	High income	227	63.1

Table 2. *Evaluation of the correlation between age and sub-dimensions of the scale*

		Age	
		r	**p**
Health Perception Scale	**Control center**	**0.145**	**0.006**
	Precision	0.114	0.030
	Importance of health	0.089	0.092
	Self-awareness	0.042	0.431
	Total	0.206	0.000
Health Literacy Scale	Access to information	-0.021	0.691
	Understanding information	-0.193	0.000
	Appraisal/Evaluation	-0.127	0.016
	Apply/use	-0.072	0.173
	Total	-0.133	0.011

Table 3. *Evaluation of sub-dimensions of scale among income levels*

		Income			
		Low	**Normal**	**High**	**p**
		Avg±SD	**Avg±SD**	**Avg±SD**	
Health perception scale	Control center	12.61±4.12	13.94±3.75	12.85±3.16	0.036
	Precision	11.93±3.36	12.79±2.93	11.74±3.17	0.040
	Importance of health	11.21±1.95	10.75±2.08	11.04±2	0.391
	Self-awareness	11.25±1.99	11.19±1.93	11.01±1.86	0.592
	Total	47±6.65	48.68±4.95	46.64±5.25	0.018
Health literacy scale (median)	Access to information	21.04±3.73 (22)	18.99±4.45 (20)	21.44±3.2 (22)	0.000
	Understanding information	29.54±4.46 (30)	24.68±6.72 (25)	29.52±4.36 (31)	0.000
	Appraisal/Evaluation	33.11±5.16 (33)	29.52±7.59 (31)	33.5±5.12 (34)	0.000
	Apply/use	21.07±3.08 (21.5)	18.51±4.6 (20)	20.67±3.28 (21)	0.001
	Total	104.75±13.53 (108)	91.69±21.24 (96)	105.12±12.7 (108)	0.000

Table 4. *Evaluation of the correlation between the health perception scale and health literacy scale sub-dimensions*

Health Literacy Scale		**Health Perception Scale**				
		Control center	**Precision**	**Importance of health**	**Self-awareness**	**Total**
Access to information	r	-0.239	-0.329	0.146	0.203	-0.219
	p	0.000	0.000	0.005	0.000	0.000
Understanding information	r	-0.269	-0.344	0.132	0.139	-0.274
	p	0.000	0.000	0.012	0.008	0.000
Appraisal/Evaluation	r	-0.284	-0.378	0.174	0.225	-0.258
	p	0.000	0.000	0.001	0.000	0.000
Apply/Use	r	-0.220	-0.404	0.275	0.186	-0.209
	p	0.000	0.000	0.000	0.000	0.000
Total	r	-0.302	-0.425	0.206	0.220	-0.287
	p	0.000	0.000	0.000	0.000	0.000

effectively, prioritizing their health, and maintaining realistic perceptions of their health (p1<0.01, p2<0.01, p3<0.05, p4<0.01, respectively).

It has been determined that individuals with low health literacy face challenges in accessing and comprehending medical information (p_1<0.01, p_2<0.01, respectively). Table 4 provides the correlation between the scales.

Discussion

The study identified a significant negative correlation between increasing age and health literacy, corroborating findings that individuals over 65 exhibit a lower understanding of medical knowledge. Intriguingly, this age group maintained positive thoughts about their health conditions despite lower health literacy. Addressing the unique health literacy needs of older individuals is crucial for promoting informed decision-making and self-management of chronic illnesses.

The socio-economic structure is an important factor in accessing knowledge about health literacy. Among participants aged 65–70, the health literacy levels of low-income individuals were 1.95 times lower than those of low-income owners. Similarly, it has been shown that low-income individuals benefit less from healthcare services and have a lower understanding of medical knowledge[15].

In their cohort study, Kobayashi et al.[16] found that internet access was significantly associated with increased health literacy, particularly among those with higher socio-economic status. The study also revealed that 15.6% of participants had low income, while 63.1% had high income. Interestingly, individuals with normal income reported lower perceptions of their general health than those with high income. It has been demonstrated that individuals with lower socio-economic status have lower health literacy levels than those with higher socio-economic status. Therefore, it is likely that those who are at risk of social inequalities will have lower health literacy levels.

Schaeffer et al.[17] used the Health Literacy Scale European Union Questionnaire (HLS-EU-Q) with 2000 participants. They found that 66% had advanced education levels. The study also revealed that higher education students had significantly higher health literacy. Protheroe et al.[18] used the Newest Vital Sign with 972 participants and found that 28.5% had low health literacy levels. It is important to note that individuals with lower levels of education may face more significant challenges in accessing accurate health information. Our study found that 3.3% of participants were illiterate, 25.3% had completed high school, and 47.5% had completed university. Notably, university graduates demonstrated a significantly higher level of health literacy than the other groups. Additionally, a positive correlation was observed between education level and health literacy. Medical information sources and access methods are well-known with the rise in education levels.

The role of health perception in managing chronic diseases is significant. Kolac[19] discovered a positive correlation between education level and health perception. Similarly, Yilmaz et al.[20] demonstrated a positive correlation between individuals' education level and health perception. Our study found that illiterate individuals had lower general health perceptions than other groups. Individuals are more likely to engage in positive health behaviors as education levels increase. The level of education has a positive impact on people's health behaviors and perceptions. Therefore, higher education levels are expected to lead to better health perception.

It has been found that inadequate information can misinterpret health conditions. It is predicted that an increase in literacy levels will lead to more realistic assessments of one's health.

This study investigates the intricate relationship between health literacy and the perceptual dynamics among individuals grappling with chronic illnesses. The findings underscore that advancing age, lower educational attainments, and diminished income levels are restrictive factors for this demographic. A positive correlation emerges, demonstrating that heightened educational levels correspond to an augmented health perception.

A pivotal conclusion drawn from this exploration is the imperative role of enhancing health literacy to foster improved compliance with treatment regimens and facilitate informed management of chronic conditions. This research substantiates the proactive engagement of individuals with chronic diseases in seeking and leveraging reliable information about their health.

Furthermore, recognizing the unique challenges faced by individuals with chronic illnesses, particularly during their interactions at family medicine outpatient clinics, is paramount. Allocating additional time for patients to articulate their concerns and extending tailored support, especially to those with low health literacy, becomes a crucial aspect of holistic healthcare provision. The directional focus towards precise and credible resources, coupled with the provision of written and visual aids, emerges as an effective strategy to augment patient understanding.

The research was conducted at the family medicine outpatient clinic of a training and research hospital. The suggestion is that conducting similar studies in multiple centers would provide a more comprehensive understanding of the relationship between health literacy and the perception of individuals with chronic illnesses.

In summary, the study emphasizes the importance of addressing health literacy to improve the perception, compliance, and overall health management of individuals with chronic illnesses, with specific attention to demographic factors and the role of education.

Ethical Approval

Ethics Committee Approval: Ethics committee approval was obtained from the Ministry of Health Istanbul Gaziosmanpasa Training and Research Hospital Clinical Research Ethics Committee; date: 23.09.2020; no: 159.

References

1. Hajat C, Stein E. The global burden of multiple chronic conditions: A narrative review. Prev Med Rep. 2018;12:293–284.
2. Essue BM, Laba M, Knaul F, Chu A, Minh HV, Nguyen TKP, et al. Economic burden of chronic health and injuries for households in low and middle income countries. In: Jamison DT, Gelband H, Horton S, editors. Disease control priorities: improving health and reducing poverty. Washington (DC): The international bank for reconstruction and development;2017: Chapter 6.
3. Bakan A, Yıldız M. 21–64 yaş grubundaki bireylerin sağlık okuryazarlık düzeylerinin belirlenmesine ilişkin bir çalışma. Sağlık ve Toplum. 2019;29(3):40–33.
4. Ishikawa H, Yano E. Patient health literacy and participation in the healthcare process. Health Expect. 2008;11(2):113–22.
5. Tokuda Y, Doba N, Butler JP, Paasche-Orlow MK. Health literacy and physical and psychological wellbeing in Japanese adults. Patient Educ Couns. 2009;75(3):411–7.
6. Senol V, Cetinkaya F, Unalan D, Balci E, Oztürk A. Determinants of selfrated health in general population in Kayseri, Turkey. Türkiye Klinikleri J Med Sci. 2010;30(1):96–88.
7. Valaitis RK, O'Mara L, Wong ST, Macdonald M, Murray N, Misener RM, et al. Strengthening primary health care through primary care and public health collaboration: the influence of intrapersonal and interpersonal factors. Prim Health Care Res Dev. 2018;19(4):391–378.
8. Yalnızoğlu Caka S, Topal S, Karakaya Suzan O, Cınar N, Altınkaynak S. Hemşirelik öğrencilerin sağlık algısı ile özgüvenleri arasındaki ilişki. J Hum Rhythm. 2017;3(4):203–198.
9. Klein Velderman M, Crone MR, Wiefferink CH, Reijneveld SA. Identification and management of psychosocial problems among toddlers by preventive child health care professionals. Eur J Public Health. 2010;20(3):8–332.
10. Wortman J, Lucas RE, Donnellan MB. Stability and change in the big five personality domains: evidence from a longitudinal study of Australians. Psychol Aging. 2012;27(4):867–74.
11. Aras Z, Temel Bayık A. Sağlık okuryazarlığı ölçeği'nin türkçe formunun geçerlik ve güvenirliğinin değerlendirilmesi. Florence Nightingale Hemşirelik Dergisi. 2017;25(2):94–85.
12. Kadıoğlu H, Yıldız A. Sağlık algısı ölçeği'nin türkçe çevriminin geçerlilik ve güvenilirliği. Türkiye Klinikleri Journal of Medical Sciences. 2012;32(1):53–47.
13. Diamond JJ, Becker JA, Arenson CA, Chambers CV, Rosenthal MP. Development of a scale to measure adults' perceptions of health: priliminary findings. Journal of Community Psychology. 2007;35(5):557–61.
14. Toçi E, Burazeri G, Kamberi H, Jerliu N, Sorensen K, Brand H. Socio-economic correlates of functional health literacy among patients of primary health care in Kosovo. Public Health. 2014;128(9):848–842.
15. Vogt D, Schaeffer D, Messer M, Berens EM, Hurrelmann K. Health literacy in old age: results of a German cross-sectional study. Health Promot Int. 2018;33(5):747–739.
16. Kobayashi LC, Wardle J, Von Wagner C. Internet use, social engagement and health literacy decline during ageing in a longitudinal cohort of older English adults. J Epidemiol Community Health. 2015;69(3):278–83.
17. Schaeffer D, Berens EM, Vogt D. Health Literacy in the German Population. Dtsch Arztebl Int. 2017;114(4):60–53.
18. Protheroe J, Whittle R, Bartlam B, Estacio EV, Clark L, Kurth J. Health literacy, associated lifestyle and demographic factors in adult population of an English city: a cross-sectional survey. Health Expect. 2017;20(1):119–112.
19. Kolac N, Balci AS, Sisman FN, Atacer BE, Dincer S. Health perception and healthy lifestyle behaviors in factory workers. Bakırköy Tıp Dergisi. 2018;14:267–74.
20. Yılmaz AT, Culha I, Kersu O, Gumus D, Unsal A, Kosgeroglu N. Cerrahi hastalarının sağlık algıları ve etkileyen faktörler. J Acad Soc Sci. 2018;68:99–89.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Coping Methods of Women Aged 15-49 with Dysmenorrhea

15-49 Yaş Aralığındaki Kadınların Dismenore ile Başetme Yöntemleri

Ozlem Karabulutlu[1], Melike Yildiz[2]

[1]Department of Midwifery, Faculty of Health Sciences, Kafkas University; [2]Kars Sarikamis District State Hospital, Kars, Türkiye

ABSTRACT

Aim: *This research was conducted in a descriptive type to determine the coping methods with dysmenorrhea used by women between the ages of 15–49.*

Material and Method: *The study population consisted of women aged 15–49 residing in a city in the north eastern region of Türkiye. The study sample consisted of 424 women who agreed to participate in the research from November to December 2020. "Descriptive Information Form" and "Dysmenorrhea Affected Scale" were used to obtain the study data. The research data was collected through an online interview.*

Results: *The mean age of women was 26.7±7.5 years. It was determined that 34.7% of the participants consulted a physician due to dysmenorrhea, and irritability, groin pain, and breast tenderness were the most common symptoms accompanying dysmenorrhea. Applying heat to the abdomen, sleeping, and drinking herbal teas were determined as the most common methods used by women to cope with dysmenorrhea. The average score on the scale is 129.69±26.82, which is above average. In the case of menstrual pain, there is a statistically significant difference between the use of analgesics and the level of dysmenorrhea (p<0.001). It was determined that there was a positive, substantial, and low-level relationship between the severity of dysmenorrhea pain and the level of dysmenorrhea affected (r=0.365; p<0.001).*

Conclusion: *More than half of the women participating in the study were found to use medication to cope with dysmenorrhea. The method of applying hot to the abdomen was determined as the most common method used by the women participating in the study in coping with dysmenorrhea. The following can be suggested: Counseling women by health personnel on issues such as the adverse effects of dysmenorrhea and coping methods.*

Key words: *dysmenorrhea; coping methods; reproductive age*

ÖZET

Amaç: *Araştırma, 15–49 yaş aralığındaki kadınların dismenore ile baş etmede kullandıkları yöntemleri belirlemek amacıyla tanımlayıcı tipte yapılmıştır.*

Materyal ve Metot: *Araştırmanın evrenini, Türkiye'nin kuzeydoğu bölgesinde yer alan bir ilde ikamet eden 15–49 yaş grubu kadınlar oluşturmuştur. Araştırmanın örneklemini ise, Kasım–Aralık 2020 tarihinde araştırmaya katılmayı kabul eden 424 kadın oluşturmuştur. Çalışmanın verilerini elde etmek için; "Tanımlayıcı Bilgi Formu" ve "Dismenore Etkilenen Ölçeği" kullanılmıştır. Araştırmanın verileri çevrimiçi görüşme yoluyla toplanmıştır.*

Bulgular: *Kadınların yaş ortalaması 26,7±7,5'dir. Katılımcıların %34,7'sinin dismenore sebebiyle doktora başvurduğu ve sinirlilik halinin, kasık ağrısının, memelerde hassasiyetin dismenoreye en çok eşlik eden semptomlar olduğu bulunmuştur. Karına sıcak uygulama, uyuma, bitkisel çaylar içme ise kadınların dismenore ile baş etmede en çok kullandıkları yöntemler olarak belirlenmiştir. Ölçeğin ortalama puanı 129,69±26,82 olup bu puan ortalamanın üzerindedir. Menstrual ağrı durumunda analjezik kullanımı ile dismenore etkilenmişlik düzeyi arasında istatistiksel olarak anlamlı bir fark bulunmaktadır (p<0,001). Dismenore nedeniyle doktora başvurma durumu ile dismenore etkilenmişlik düzeyi arasında anlamlı bir farklılık bulunmaktadır (p<0,001). Dismenore ağrı şiddeti ile dismenore etkilenmişlik düzeyi arasında pozitif yönlü anlamlı ve düşük düzeyde bir ilişki olduğu belirlenmiştir (r=0,365; p<0,001).*

Sonuç: *Çalışmaya katılan kadınların yarısından fazlasının dismenore ile baş etmek için ilaç kullandığı bulunmuştur. Karına sıcak uygulama yöntemi, çalışmaya katılan kadınların dismenore ile baş etmede en sık kullandığı yöntem olarak belirlenmiştir. Sağlık personelinin dismenorenin olumsuz etkileri, baş etme yöntemleri gibi konulara yönelik kadınlara danışmanlık yapması önerilebilinir.*

Anahtar kelimeler: *dismenore; baş etme yöntemleri; üreme çağı*

İletişim/Contact: *Ozlem Karabulutlu, Faculty of Health Sciences, Department of Midwifery, Kars, Türkiye* • ***Tel:*** *0532 178 10 81* • ***E-mail:*** *okarabulutlu@gmail.com* • ***Geliş/Received:*** *31.05.2023* • ***Kabul/Accepted:*** *03.04.2024*

ORCID: *Özlem Karabulutlu: 0000-0001-5307-5186* • *Melike Yıldız: 0000-0002-6855-7660*

Introduction

Pain is one of the most frequently experienced symptoms accompanying infection and bleeding in women and is one of the most prominent reasons for applying to the gynecology outpatient clinic[1]. Although menstruation is a physiological condition seen in women's lives, problems seen during menstruation negatively affect the person's quality of life. Dysmenorrhea is the most important and common of these problems[2].

Dysmenorrhea is a word of Greek origin. Dys (Dis) means painful, abnormal; the meno is the month; rhea (re) means flow[3]. This is when the individual has menstrual pain that interferes with regular activity and requires medication. Dysmenorrhea is briefly defined as "painful menstruation"[4,5]. Dysmenorrhea is the most common gynecological problem[6]. Uterine contractions, which disrupt blood flow in the uterus and pain during menstruation, cause the pain of dysmenorrhea[7].

Dysmenorrhea can be seen in every woman regardless of age and race, but adolescents are more common in younger women[8]. Dysmenorrhea is a condition that starts 1–2 years after menarche and continues regularly every month until the age of 40s[9]. Dysmenorrhea affects the quality of life and is associated with social situations, such as limited mobility, absenteeism from school and work, increased accidents, and economic losses[10,11].

It has also been found that dysmenorrhea reduces sleep quality[1]. However, women with dysmenorrhea were found to have higher body image disorders and depression symptoms. In addition, when evaluated in terms of nutritional disorders, it was determined that women with severe dysmenorrhea were a risk group[12].

Dysmenorrhea is the most common gynecological problem before menopause, with a rate of 55–93%[2,13]. A study determined that the individuals who experienced this problem the most were in the 16–17 age group[2]. Dysmenorrhea prevalence rates vary in many countries. For example, it was recorded as 28% in Mexico, 60% in Canada, 53% in New Zealand, and 55.5–95.6% in Türkiye[14,15].

Today, most treatments that are not modern but have holistic approaches are considered Complementary and Alternative Medicine (CAM)[6,16]. According to Keskin et al. (2016), CAM use is 41%-48.5% worldwide and 12.6–76% in Türkiye for various reasons[17]. In general, many CAM methods are used to treat dysmenorrhea. There are many old and new CAM applications in the form of acupuncture, mind-body-based therapies, body-based and manipulative therapies, diet, vitamins and minerals, and herbal therapies[1,18]. It is stated that with a rate of 80.9%, massage, and hot application are the most used methods to coping with dysmenorrhea[19].

Studies on the use of women's preferred coping methods with dysmenorrhea were found to be limited in the literature review. Therefore, this study aims to determine the methods preferred by women to cope with dysmenorrhea. It is thought that this will contribute to health professionals' knowledge about these methods. Based on this information, this study was conducted to determine the coping methods with dysmenorrhea of women aged 15–49 years.

Material and Methods

Study Type and Location

This research was carried out in November-December 2020 in a descriptive manner on women between the ages of 15–49 living in a city in the northeastern region of Türkiye. The research data was collected through an online interview.

Population and Sample of the Research

The study population consisted of women aged 15–49 residing in a city in the northeastern region of Türkiye. The central population of Kars province is 116,712 people as of 2019, and 57,796 of this population consists of women. This number corresponds to 49.52% of the total population[20]. While calculating the study sample, it was estimated that the number of women aged 15–49 in Kars would be between 25,000 and 50,000 people. It has been determined that the minimum number of samples to be taken for a population is 381 people, with a margin of error of 0.05 and a 95% confidence interval[21]. Considering that there may be deficiencies in the data collection forms in this study, it was decided to take an additional sample of 10%. After this procedure, it was calculated that a minimum of 419 people should be included in the study. After the data collection phase, 451 people were reached. Still, when the data were analyzed, 27 participants were excluded from the study due to missing and incorrect information in the data form. After these procedures, the study sample consisted of 424 people.

Variables of the Study: Demographic characteristics of women constitute the independent variable of the research, and, the methods used by women to cope with dysmenorrhea and the level of being affected by dysmenorrhea constitute the dependent variable of the study.

Data Collection Tools

In the study, together with the data obtained, the "Descriptive Information Form" and the "Dysmenorrhea Activity Scale" as a result of the literature scanned by the researcher were used for women between the ages of 15–49.

* ***Introductory Information Form:*** The researcher created the relevant form due to the literature review[6,22,23]. This consists of 29 questions such as age, marital status, education level, age at first menstruation, height, weight, duration of menstruation, alcohol and cigarette use, current gynecological disease conditions, symptoms accompanying dysmenorrhea, methods used to cope with dysmenorrhea of women between the ages of 15–49.

* ***Dysmenorrhea Effectiveness Scale:*** The Dysmenorrhea Effectiveness Scale (DES), whose validity and reliability study were conducted by Gün (2014), was designed to determine women's problems and coping methods during menstrual pain. It consists of a total of 39 items and 11 sub-dimensions. The scale's Cronbach's Alpha coefficient is 0.90. Participants evaluate each item on a 5-score Likert-type scale ranging from "strongly disagree (1)" to "strongly agree (5)". As the score obtained from the scale increases, the level of being affected by dysmenorrhea also increases. The lowest score that can be obtained from the scale is 39, and the highest score is 195. In the study, the average score on the scale was 129.69±26.82 (Minimum=67, Maximum=179), which is above average.

Dysmenorrhea effectiveness scale sub-dimensions and the items they contain are as follows:

1. Health perception and health management pattern (Items: 6, 16)
2. Nutrition and metabolic pattern (Items: 22, 27, 29)
3. Excretion pattern (Items: 2, 5)
4. Activity-exercise pattern (Items: 8, 10, 13, 15)
5. Cognitive-perceptual pattern (Items: 25, 31, 33)
6. Sleep-rest pattern (Items: 34, 36, 38)
7. Self-perception and self-concept pattern (Items: 4, 9, 11, 12, 14, 17)
8. Role relationship pattern (Items: 1, 3, 7)
9. Sexual reproduction pattern (Items: 18, 20)
10. Coping, stress tolerance pattern (Items: 23, 35, 37, 39)
11. Value belief pattern (Items: 19, 21, 24, 26, 28, 30, 32)[3].

Criteria for Inclusion in the Research

- Being between the ages of 15–49,
- Not currently pregnant and continuing menstrual cycle,
- Having dysmenorrhea,
- Agree to participate in the study.

Collection of Data

The research data were collected between November and December 2020 through an online interview. The researcher gave information about the purpose of the research via Google Forms, and volunteers were included in the study.

Evaluation of Data

Data analysis was done with the IBM Statistical Package for Social Sciences (SPSS) program version 23.0 package program. Arithmetic mean, standard deviation and percentage parameters were used in data analysis. Apart from this, parametric tests were used for variables with normal distribution, and nonparametric tests were used for variables that did not show normal distribution and $p<0.05$ was accepted as significant.

Ethical Aspect of Research

To conduct the research, ethics committee approval dated 30.10.2020 with number 2020/9 was obtained from the Non-Interventional Studies Ethics Committee of the Faculty of Health Sciences of a university in the eastern Anatolia region. For the measurement tool to be used in the research, permission was obtained via e-mail. The women included in the study were informed about the research and, the ethical principles, including the "Respect for Autonomy," were fulfilled after the "Informed Consent" principle was taken from those who voluntarily participated in the study. Ethical principles in the Declaration of Helsinki were complied with in the study.

Results

It was determined that the age range of the study participants varied between 18 and 49, and the sample mean was 26.7±7.5. When the Body Mass Index of the sample was examined, the mean was 23.1±3.7. 66.7% of the participants are single individuals. When the education level is reviewed, it has been determined that the education level of the majority (74.8%) is higher

education. 19.3% of the participants smoke, and 6.4% use alcohol. The rate of those consuming caffeinated beverages daily was 84.4%.

When the continuous variables of menstruation were examined, it was seen that the age of first menstruation varied between 11 and 16, and the mean was 13.6±1.2. When the pain intensity seen during the menstrual period was asked to be evaluated between 0–10, it was determined that the average pain score was 6.2±2.5.

When the categorical data on menstruation is examined, it is seen that the menstrual cycle of 73.8% of the sample is between 22 and 35 days. More than half of the sample (53.1%) had a menstrual period of 5 days or less. While 72.9% of the participants in the study experience pain in very little of the menstrual period, and 13% experience menstrual pain throughout. In addition, 34.7% of the sample applied to a physician because of menstrual pain. While the rate of those who have any gynecological disease is 26.6%, the rate of those who have menstrual pain in their family is 68.9%. 53.3% of the sample stated that they use painkillers to cope with menstrual pain. The rate of those who participated in training programs related to the menstrual period was 66.7% (Table 1).

In the study, when the symptoms accompanying dysmenorrhea were examined, it was found that 75.9% were nervous, 75% had groin pain, and 54% had breast tenderness, respectively. In our study, when we look at the methods used to relieve the severity of pain due to dysmenorrhea, hot application to the abdomen comes first with 64.1%. (Table 2).

When the dysmenorrhea affectation scale averages are examined according to marital status, it was determined that the average rank of the "single" individuals was 221.49. The average rank of the "married" individuals was 194.46, and this difference between the rankings was determined to be at a statistically significant level (Z=-2.140; p<0.05). According to this finding, the level of being affected by dysmenorrhea in "single" individuals is significantly higher than that of "married" individuals. When the level of being affected by dysmenorrhea in terms of educational status of the participants was examined, it was observed that the average rank of those with "primary education" was 198.09, 175.19 for those with "secondary

Table 1. *Distribution of data regarding categorical variables of menstruation (n=424)*

Variable	Category	n	%
Menstruation Cycle	Less than 21 days	88	20.8
	22-35 days	313	73.8
	More than 36 days	23	5.4
Menstruation Period	5 days and less	225	53.1
	6 days and more	199	46.9
How much pain is experienced during the menstrual period	Very few	309	72.9
	Approx half	60	14.1
	All	55	13.0
Seeing a doctor because of painful menstruation	Yes	147	34.7
	No	277	65.3
The presence of gynecological disease	Available	117	27.6
	n/z	307	72.4
Individuals with a family history of painful menstruation	Available	292	68.9
	n/z	132	31.1
Painkillers for menstrual pain	Yes	226	53.3
	No	198	46.7
The status of training for the menstrual period	Yes	283	66.7
	No	141	33.3

Table 2. *Problems experienced in the menstrual cycle and distribution of coping methods (n=424)*

Symptoms Accompanying Dysmenorrhea	n	%
Diarrhea	148	34.9
Constipation	53	12.5
Nausea	170	40.1
Breast tenderness	229	54.0
Back pain	196	46.2
Groin pain	318	75.0
Menstrual cramps	124	29.2
Headache	141	33.2
Insomnia	62	14.6
Weakness	209	49.3
Unrest	202	47.6
Nervousness	322	75.9
Susceptibility	208	49.1
Clot formation in menstrual blood	191	45.0
Awkwardness	36	8.5
Focus problem	99	23.3
Other	28	6.6
Coping Methods During Menstrual Pain*		
Walk	62	14.6
Hot shower	145	34.2
Hot application to the abdomen	272	64.1
Massage	131	30.9
Herbal teas	193	45.5
Dealing with other things will make them forget the pain	129	30.4
Sleeping	216	50.9
Making dietary changes	20	4.7
Meditation, yoga or breathing exercises	17	4.0
Using pain relievers	189	44.6
Other	19	4.5

* Participants marked more than one option.

education" and 221.19 for those with "higher education" and, the difference between the groups was found to be statistically significant (X^2=7.258); p<0.05). As a result of the paired comparisons, it was determined that there was a considerable difference between those whose education level was "Secondary Education" and those who had "Higher Education." According to this finding, the level of being affected by dysmenorrhea of individuals with a "higher education" level is significantly higher than the group with a "secondary education" level. When the difference in being affected by dysmenorrhea according to smoking status is examined, it was determined that the mean rank of the smoking group was 228.57, and the mean rank of the non-smoker group was 208.65. It was determined that there was a difference between the two groups in terms of mean rank, but this difference was statistically insignificant (Z=-1.322; p>0.05). When the level of being affected by dysmenorrhea according to the alcohol consumption status of the sample was examined; it was determined that the average rank of the alcohol-consuming group was 215.50 and the non-alcoholic group was 212.30. There was no statistically significant difference between the two groups in terms of the level of being affected by dysmenorrhea (Z=-0.131; p>0.05). When the levels of exposure to dysmenorrhea of the groups consuming and not consuming caffeinated beverages daily were examined, it was determined that the average rank of the group consuming caffeinated beverages was 220.15, and the group that did not consume was 171.03. In the examination, it was determined that this difference between the two groups was statistically significant (Z=-2.993; p<0.05). According to this finding, those who consume caffeinated beverages are more affected by dysmenorrhea than those who do not consume caffeinated beverages (Table 3).

When the relationship between age and the level of being affected by dysmenorrhea is examined, It was determined that there was an inverse and low-level correlation between the two variables, but this correlation was not statistically significant (r=-0.085; p>0.05). When the relationship between body mass index (BMI) and being affected by dysmenorrhea is examined; There was a positive, but not statistically significant, relationship between these two variables (r=0.010; p>0.05). When the relationship between the age of first menstruation and the level of being affected by dysmenorrhea is examined; no statistically significant relationship was found between these two variables (r=-0.063; p>0.05). When the relationship between the perceived pain intensity during the menstrual period and the level of being affected by dysmenorrhea is examined; it was observed that there was a significant positive and low-level relationship (r=0.365; p<0.001). According to this finding; As perceived pain increases, the level of being affected by dysmenorrhea also increases (Table 4).

When the level of being affected by dysmenorrhea is examined according to the monthly menstrual cycle; no statistically significant difference was found between the groups (X^2=1.045; p>0.05). Similarly, the level of being affected by dysmenorrhea did not differ according to the duration of menstruation (Z=-0.023; p>0.05). While the average rank of those who experience pain in a tiny part of their menstrual period is 199.00, the average rank of those who experience pain in half of their menstrual period is 216.21, and the rank of those who experience pain during the whole period is 284.30. It was determined that the mean ranks of those who applied to a physician due to painful menstruation were higher than the mean ranks of those who did not consult a physician (248.58 and 193.35, respectively), and this difference was statistically significant (Z=-4.417; p<0.001).

Table 3. *Comparison of women's level of affected by dysmenorrhea according to some demographic variables (n=424)*

Variable	Category	Average rank	Significance
*Civil Status	Married	194.46	Z= -2.140
	Single	221.49	p=.032
**Education	Primary	198.09	X^2=7.258
	Secondary	175.19	p=.027
	Higher	221.19	
*Smoke	Yes	228.57	Z= -1.322
	No	208.65	p=.186
*Alcohol	Yes	215.50	Z= -0.131
	No	212.30	p=.895
*Daily caffeinated beverage cons.	Yes	220.15	Z= -2.993
	No	171.03	p=.003

* Normal distribution of the variable in subcategories could not be achieved.
* Z: Mann-Whitney U Test
** Kruskal-Wallis

Table 4. *The relationship of level of affected by dysmenorrhea with some variables*

Variable	n	r	r^2	p
Age	424	-0.085	0.007	0.080
BMI	424	0.010	0.000	0.825
First menstruation age	424	0.063	0.003	0.199
Perceived intensity of pain during menstruation	424	0.365	0.133	0.000

Pearson correlation

According to this finding; As the level of being affected by dysmenorrhea increases, the application to the physician increases. The presence of gynecological disease in the individual seems to be a significant finding in terms of the level of being affected by dysmenorrhea. While the mean rank of the group with gynecological disease was 239.75, the mean rank of the group without the disease was determined as 202.12, and the difference was found to be significant (Z=-2.827; p<0.05). When the level of being affected by dysmenorrhea is examined according to the presence of someone in the family who has had a painful period; there is no significant difference between the groups (p>0.05). When the level of being affected by dysmenorrhea according to the use of painkillers for menstrual pain was examined; it was determined that the mean ranks of those who used painkillers for menstrual pain were higher than those who did not (237.40 and 184.08, respectively), and this difference was statistically significant (Z=-4.471; p<0.001). According to this finding; individuals with a high level of being affected by dysmenorrhea have a higher level of using painkillers for menstrual pain. When the level of being affected by dysmenorrhea is examined according to the educational status regarding the menstrual period, there was no difference between those who got an education and those who did not (Z=-0.112; p>0.05) (Table 5).

Discussion

Dysmenorrhea is one of the most common problems during menstruation. This research was conducted in a descriptive type to determine the coping methods with dysmenorrhea used by women between the ages of 15–49. The discussion results are given below.

It was determined that the age of menarche of the individuals participating in this study ranged from 11 to 16. The mean age was 13.6, and there was no statistically significant difference between the age of menarche and the level of being affected by dysmenorrhea. Karabulutlu (2020), in his study, determined that 68.4% of nursing students were between 12–14 years of age at menarche. In addition, the difference between dysmenorrhea and age at menarche was statistically insignificant[24]. Demirci (2017) investigated the CAM methods used to cope with dysmenorrhea, found the mean age at menarche to be 12.97 and found that the age of menarche and the use of CAM in dysmenorrhea were not related[1]. Similarly, in the study of Erenel and Şentürk (2007) and Yüce (2018), it was stated that there was no statistically significant difference between the incidence of dysmenorrhea and the age of menarche[2,14]. The results of our study and other study results show parallelism.

It was found that more than half of the women with dysmenorrhea who participated in the study (66.7%)

Table 5. *Comparison of the level of affected by dysmenorrhea, according to some menstrual characteristics*

Variable	Category	Average rank	Significance
**Menstruation Cycle	Less than 21 days	200.65	X^2=1.045 p=.593
	22-35days	215.75	
	36 days and more	213.67	
*Menstruation Period	5 days and less	212.37	Z=-.023
	6 days and more	212.65	p=.982
**How much pain is experienced during the menstrual period	Very few	199.00	X2=22.697 p=.000
	Approx. Half	216.21	
	All	284.30	
*Seeing a doctor because of painful menstruation	Yes	248.58	Z=-4.417
	No	193.35	p=.000
*The presence of gynecological disease	Available	239.75	Z=-2.827
	n/a	202.12	p=.005
*Individuals with a family history of painful menstruation	Available	220.11	Z=-1.903
	n/a	195.66	p=.057
*Painkillers for menstrual pain	Yes	237.40	Z=-4.471
	No	184.08	p=.000
*The status of training for the menstrual period	Yes	212.97	Z=-.112
	No	211.56	p=.911

* Normal distribution could not be achieved in the subcategories of the variable.
* Z: Mann-Whitney U Test
** Kruskal-Wallis

were single. When the dysmenorrhea affectation scale averages were examined according to marital status, it was determined that the average rank of the "single" individuals was 221.49, and the average rank of the "married" individuals was 194.46. This difference between the rankings was determined to be at a statistically significant level ($p<0.05$). In our study, it was found that single individuals were more affected by dysmenorrhea than married individuals. According to the study of Güngörmüş and Kiyak (2012); it was determined that single women had higher CAM usage rates, but there was no statistically significant difference[25]. The higher use of CAM in singles may be due to the desire of these groups to get results in the short term, the fact that they are a group more affected by the environment, and the fact that they are the group most affected by the increase in CAM popularity seen all over the world in recent years. It can be said that there is a need for more studies examining the relationship between CAM use and marital status.

When the study participants' body mass index (BMI) was examined; an average of 23.1 kg/m^2 was reached. In addition, in this study, a non-significant relationship was observed between BMI and the level of being affected by dysmenorrhea. In Erdoğan's (2013) study; the average BMI of the participating individuals was determined as 22.18 kg/m^2, and it was determined that the rate of dysmenorrhea was higher in thin individuals[26]. Metin and Kahyaoğlu Süt (2021), in their study, found the BMI value of women with primary dysmenorrhea to be 22.73. It was stated in the study that an increase in facial fat would reduce the risk of dysmenorrhea[27]. Zurawiecka and Wronka (2018) conducted a study on university students aged 19–25. They stated that dysmenorrhea is more common in women with BMI <18.5 (thin) and BMI >25 (overweight)[28]. The results of the research are different. It is thought that it may vary depending on variables such as geography and participant age groups.

In the study, the mean menstrual cycle of women with dysmenorrhea was found to be 22–35 days, with a rate of 73.8%. No statistically significant difference was found between the menstrual cycle and the level of being affected by dysmenorrhea. This was determined as 28–33 days in the study of Karabulutlu (2020) and 21–35 days in the study of Erdoğan (2013)[24,26]. Sönmezer (2014) found the cycle duration of the connective tissue massage group to be 28–34 days with a rate of 45.7%[29]. As a result of the research of Yüce (2018), it was determined that the incidence of dysmenorrhea is two times higher in women with irregular menstrual cycles[14]. Unlike these studies, in the study of Şahin et al. (2015) and Sönmezer (2014), it was found that there is no correlation between experiencing dysmenorrhea and menstrual cycle pattern[23,29]. These results were different. It is thought that they may vary depending on variables such as geography and participant age groups.

In the study, more than half (53.1%) of women with dysmenorrhea had a menstrual period of 5 days and less than five days. In the study, no significant difference was found between the level of being affected by dysmenorrhea and the duration of menstruation. In the study conducted by Yilmaz and Yazici (2010), it was found that the duration of menstruation (4–6 days) and the state of experiencing dysmenorrhea[30].

The pain intensity experienced by the individuals participating in the study during the menstrual period was evaluated between 0–10, and the average was found to be 6.2. In addition, according to the study, it was revealed that the severity of pain in the menstrual period and the level of being affected by dysmenorrhea were related. The level of being affected by dysmenorrhea increased as the perceived pain intensity increased. In the study of Polat and Mucuk (2021), most of the participants determined the severity of pain as 5–8[31]. This was found to be 6.17 in the study of Erdogan (2013), 5.56 in the study of Demirci (2017), 6.35 in the study of Yilmaz et al. (2020), and 6.40 in the study of Gün (2014)[26,1,32,3]. Our research and other studies show similarities.

In the study, the rate of participants who received training for the menstrual period was determined to be 66.7%. Our study determined that the level of being affected by dysmenorrhea was not related to the educational status of the menstrual period. In addition, most individuals participating in the study reported that they received the training for the menstrual period from school. The study conducted by Demirci (2017) determined that most women received information about the menstrual period, and the mothers mostly gave the training. Karabulutlu (2020) found that 74.3% of the students received training on menarche, and the mother was the first source of information. In addition, Karabulutlu stated that the status of experiencing dysmenorrhea was not associated with the status of receiving training[24].

Similarly, in the study of Erenel and Şentürk (2007), it was seen that the participants received information about menarche, and mothers were the first source of this information[2]. When we look at the results, the educational status of the participants is similar to that of our study. Still, different results were obtained in our study as a source of information.

In the study, the alcohol consumption rate of the participants was found to be 6.4%. In our study, it was determined that alcohol use did not affect dysmenorrhea. In the study of Metin and Kahyaoğlu Süt (2021), the rate of alcohol use in women with primary dysmenorrhea was found to be 18%, and that of women without primary dysmenorrhea was 24%[27]. In other studies, alcohol use rates are as follows: In the study of Gün (2014), the rate of alcohol use was found to be 14.2%, and he stated that there was no significant difference between pain severity and alcohol use[3]. Findings in the study and other research results were similar, and alcohol use rates were found to be low.

The smoking rate of women with dysmenorrhea who participated in the study was found to be 19.3%. In addition, in this study, it was found that smoking was not associated with the level of being affected by dysmenorrhea. In the study of Şahin et al. (2015), it was stated that smoking status may be related to the incidence of dysmenorrhea[23]. In the study of Metin and Kahyaoğlu Süt (2021), it was found that 31% of women with primary dysmenorrhea and 25% of women without primary dysmenorrhea were smokers[27]. Yüce (2018) found in his study that there was little relationship between tobacco and addictive substance use and dysmenorrhea[14]. In the study of Şahin et al. (2015), on the other hand, it was stated that smoking is related to the individuals' dysmenorrhea[23]. Studies have shown that smoking is generally low. However, the results of the studies differ.

It was determined that 84.4% of the study participants consumed caffeinated beverages daily. In our study, the level of being affected by dysmenorrhea in individuals who consumed caffeinated beverages was found to be higher than those who did not consume caffeinated beverages. In the study of Şahin et al. (2015), it was stated that there was no significant difference between the consumption of tea, coffee and cola and the state of experiencing dysmenorrhea[23]. In the study of Gün (2014), it was stated that there was a statistically significant difference between caffeine consumption and pain intensity[3]. The results of the studies are different. It can be said that more studies are needed regarding the relationship between caffeine consumption and dysmenorrhea.

Most of the participants in the study reported that they experienced pain during menstruation. It was found that the majority (72.9%) of the women in the study experienced pain for very little of the cycle time. In addition, in our study, it was found that as the duration of pain increased, the level of being affected by dysmenorrhea also increased. As a result of the study conducted by Sönmezer (2014) on two groups, it was determined that there was pain on the first day of menstruation in both groups. There was no statistically significant difference between dysmenorrhea and the pain duration of the cycle[29]. In the study of Erenel and Şentürk (2007), it was found that 38.3% of the participants had pain that started with menstruation and had pain on the first day.[2] Similar results have been obtained in many studies[1,15,24,26].

In the study, more than half of the participants (68.9%) stated that there was a family member experiencing pain due to dysmenorrhea. In the study, it was determined that there was no significant difference between the presence of individuals with a family history of dysmenorrhea and the level of being affected by dysmenorrhea. In the literature, it has been stated that dysmenorrhea is not a hereditary condition. Still, it is also known that the presence of a family history of dysmenorrhea is associated with dysmenorrhea[2,23]. In the study of Şahin et al. (2015), it was stated that there was dysmenorrhea in the family history of students with dysmenorrhea[23]. Similarly, in the study of Erenel and Şentürk, dysmenorrhea was observed in the first-degree relatives of more than half of the students with dysmenorrhea[2]. The study by Yaşar et al. (2020) determined that dysmenorrhea in the family history did not affect dysmenorrhea[33]. According to the research results of Hailemeskel et al. (2016), the incidence of dysmenorrhea in women with a family history of dysmenorrhea was 27 times higher than in women who did not[34]. The results of our research and other studies differ.

In the study, 34.7% of women consulted a physician due to painful menstruation. In our study, it was determined that as the level of being affected by dysmenorrhea increased, the situation of individuals to consult a doctor also increased. In the study of Kuşaslan Avci and Sari (2018), the rate of consulting a physician for women with dysmenorrhea was 22.5%. It was found that there was a statistically significant relationship between the severity of pain and the state of going to the physician for dysmenorrhea and other similar reasons[35]. In the

study of Gün (2014), the rate of visiting physicians for dysmenorrhea was 17%. The study found that the severity of pain and the status of consulting a physician were related[3]. In addition, due to social and cultural reasons, it is seen that the rate of physician visits is low in countries such as India, Nigeria and Egypt[35]. The results of our research and other studies show similarities.

In the study, the rate of analgesic use by women to relieve pain was 53.3%. In the study, the use of analgesics for dysmenorrhea and the level of being affected by dysmenorrhea were examined, and it was determined that there was a statistically significant difference between drug users and non-users. In the study of Yilmaz et al. (2020), it was determined that the average pain intensity of individuals who use drugs is higher than those who do not use drugs[32]. In the study of Yilmaz and Başer (2016) and Erenel and Şentürk (2007), it was determined that the rate of receiving medical assistance in coping with dysmenorrhea was low[2,36]. Judging by these results, it can be considered that women may need training in coping with dysmenorrhea and the use of analgesics.

In the study, when the symptoms accompanying dysmenorrhea were examined; Nervousness, groin pain, breast tenderness, weakness and irritability were found, respectively. In the study of Bakir and Beji (2021), they found premenstrual syndrome and symptoms accompanying pain as fatigue (65.5%), nervousness (64.9%) and appetite changes (63.1%), respectively[37]. In the study conducted by Topel and Pehlivan (2021), the symptoms accompanying premenstrual syndrome were determined as change in appetite (73.2%), fatigue (69.5%), and depressive affect (68.3%), respectively[38]. In the study of Türkmen (2019), it was determined that students who experienced symptoms such as weakness, tenderness, and breast pain were more likely to experience dysmenorrhea than students who did not[15]. Similar and different results are obtained when our research and other studies are examined.

In our study, when we look at the methods used to relieve the severity of pain due to dysmenorrhea, hot application to the abdominal region comes first. Other methods following the hot application to the abdominal region were determined as sleeping, drinking herbal teas, using painkillers, hot showers, massage, dealing with other things that will make forget the pain and walking, respectively. In the study of Gün (2014), the most commonly used CAM method to cope with dysmenorrhea was hot application to the abdominal region (67.2%)[3]. According to Kahyaoğlu Süt et al. (2019) research results, To reduce the pain associated with dysmenorrhea, prone and fetal positions were determined as lying down (57.9%), taking a hot shower (57.6%), sleeping (57.6%), applying hot to the feet (55.5%), and applying hot to the abdomen (52.2%)[6]. In the study of Şahin et al. (2015), it was determined that more than half of the participants preferred applying hot to the feet (59.1%), sleeping-resting (58.5%) and taking analgesics (56.1%) to coping with dysmenorrhea[23]. In the study conducted by Dogan et al. (2020), it was determined that individuals with dysmenorrhea preferred lying down and resting (72%) in the first, wearing comfortable cotton clothes in the second (63%), and rubbing the abdomen region in the third (56%)[39].

Conclusion and Suggestions

It was determined that most of the women participating in the study experienced pain during the menstrual period, and the mean pain was 6.2±2.5. It was determined that the majority of women with dysmenorrhea who participated in the study were individuals with a family history of dysmenorrhea. It was determined that the women in the study had a low rate of consulting a physician in case of dysmenorrhea. In the study, nervous, groin pain, breast tenderness, weakness and irritability were determined as the most accompanying symptoms of dysmenorrhea. More than half of the women participating in the study were found to use medication to cope with dysmenorrhea. The method of applying hot to the abdomen was determined as the most common method used by the women participating in the study in coping with dysmenorrhea.

Based on the research results, the following can be suggested: Counseling women by health personnel on issues such as the negative effects of dysmenorrhea and coping methods; Informing women by Nurses with dysmenorrhea on effective coping methods and research evidence-based methods that can be used and, follow current studies.

Acknowledgment

This study was taken from the master thesis study approved by Kafkas University Institute of Health Sciences, Department of Nursing on 15.03.2022.

Conflict of Interest

There is no conflict of interest related to this study

References

1. Demirci D. Dismenore ile Baş Etmede Kullanılan Tamamlayıcı ve Alternatif Tedavi Yöntemleri. (Yüksek Lisans Tezi) . Aydın: Adnan Menderes Üniversitesi, Sağlık Bilimleri Enstitüsü, Doğum- Kadın Sağlığı ve Hastalıkları Hemşireliği Anabilim Dalı, 2017.
2. Erenel AŞ, Şentürk İ. Health High School Students Experienced Dysmenorrhoea and Their Applications. Journal of Hacettepe University School of Nursing, 2007:47–60.
3. Gün Ç. Dismenore Etkilenmişlik Ölçeğinin Geliştirilmesi. (Doktora Tezi) . İstanbul: Marmara Üniversitesi, Sağlık Bilimleri Enstitüsü, Doğum ve Kadın Hastalıkları Hemşireliği Anabilim Dalı, 2014.
4. Potur DC, Kömürcü N. Complementary Therapies for Dysmenorrhea Management/Dismenore Yonetiminde Tamamlayici Tedaviler. Journal of Education and Research in Nursing,. 2013;10(1):8–14.
5. Ayan M, Taş U, Söğüt E, Arıcı S, Karaman S, Esen M, Demirtürk F. Primer Dismenore Ağrılı Hastalarda Diklofenak Sodyum ve Parasetamol Tedavi Etkinliklerinin Vizüel Analog Skala Kullanılarak Karşılaştırılması. Ağrı Dergisi,. 2013;25(2):78–82.
6. Kahyaoğlu Süt H, Küçükkaya B, Arslan E. Primer Dismenore Ağrısında Tamamlayıcı ve Alternatif Tedavi Yöntemleri Kullanımı. Celal Bayar Üniversitesi Sağlık Bilimleri Enstitüsü Dergisi,. 2019;6(4):322–327.
7. Putri P, Mediarti D, Della Noprika D. Hubungan Tıngkat Stres Terhadap Kejadıan Dısmenore Pada Remaja Putrı. JKM. Jurnal Keperawatan Merdeka,. 2021;1(1):102–107.
8. Kilci Ş, Daşıkan Z, Muslu A. Primer Dismenore Ağrı Yönetiminde Kullanılan Tamamlayıcı ve Bütünleştirici Terapi Uygulamaları. Atatürk Üniveristesi Kadın Araştırmaları Dergisi,. 2020;1(2):70–80.
9. Topçu Akduman A, Çimen Budur O. Treatment Modalities in Primary Dysmenorrhea. Anatolian Clinic the Journal of Medical Sciences,. 2016;21(3):235–240.
10. Farotimi AA, Esike J, Nwozichi CU, Ojediran TD, Ojewole FO. Knowledge, Attitude and Healthcare-Seeking Behavior Towards Dysmenorrhea Among Female Students of A Private University in Ogun State, Nigeria. Journal of Basic and Clinical Reproductive Sciences,. 2015;4(1):33–38.
11. Taşkın L. (2020). Üreme Sisteminin Fizyolojisi. İçinde: Taşkın L, Editör. Doğum ve Kadın Sağlığı Hemşireliği. 16. Baskı, Ankara, Akademisyen Kitabevi. p:51–56.
12. Sönmezer E, Yosmaoğlu HB. Dismenoresi Olan Kadınlarda Menstruasyona Yönelik Tutum ve Stres Algısı Değişiklikleri. Türk Fizyoterapi ve Rehabilitasyon Dergisi,. 2014;25(2):56–62.
13. Temizkan S. Menstruasyon Ağrısı Olan Kadınlarda Kinezyolojik Bantlamanın ve Aerobik Egzersizin Etkileri. (Yüksek Lisans Tezi) . İstanbul: İstanbul Medipol Üniversitesi, Sağlık Bilimleri Enstitüsü, Fizyoterapi ve Rehabilitasyon Anabilim Dalı, 2020.
14. Yüce E. Adölesan Genç Kızlarda Dismenore Prevalansı, Etkileyen Faktörler ve Özbakım Deneyimleri. (Yüksek Lisans Tezi) . İstanbul: Marmara Üniversitesi, Sağlık Bilimleri Enstitüsü, Hemşirelik Anabilim Dalı, 2018.
15. Türkmen H. Üniversite Öğrencilerinde Dismenore Görülme Sıklığı ve Dismenoreye Etki Eden Faktörler. Celal Bayar Üniversitesi Sağlık Bilimleri Enstitüsü Dergisi,. 2019;6(1):39–46.
16. Çetin O. Eskişehir'de Tamamlayıcı ve Alternatif Tıp Kullanımı. Sosyoekonomi,. 2007;6(6):89–106.
17. Keskin TU, Yeşilfidan D, Adana F, Okyay P. Aydın Sağlık Yüksekokulu Öğrencilerinde Perimenstrüel Şikâyetler ve Başa Çıkma Yöntemleri. TAF Prev Med Bull,. 2016;15(5):382–388.
18. Özcebe H, Sevencan F. Çocuklarda Tamamlayıcı ve Alternatif Tıbbı Konu Alan Araştırmaların Değerlendirilmesi. Çocuk Sağlığı ve Hastalıkları Dergisi,. 2009;52(4):183–194.
19. Gün Ç, Demirci N, Otrar M. Dismenore Yönetiminde Tamamlayici Alternatif Tedavileri Kullanma Durumu, Spatula DD,. 2014;4(4):191–197.
20. Web: https://www. nufusu. com/il/kars-nufusu (Erişim Tarihi:28. 10. 2020).
21. Yazıcıoğlu Y, Erdoğan S. SPSS Applied Scientific Research Methods. Ankara, Detay Publishing, 2004.
22. Erdoğan M, Özsoy S. Genç Kızların Dismenore İçin Kullandığı Non-Farmakolojik Yöntemler. Maltepe Tıp Dergisi,. 2012;4(4):13–14.
23. Şahin S, Kaplan S, Abay H, Akalın A, Demirhan İ, Pınar G. Üniversite Öğrencilerinde Dismenore Yaşama Sıklığı ve Etkileyen Faktörlerin Değerlendirilmesi. Ankara Sağlık Bilimleri Dergisi,. 2015;4(1):25–44.
24. Karabulutlu Ö. Hemşirelik Öğrencilerinin Dismenore Yaşama Durumları ve Dismenore ile Baş Etmeye Yönelik Uygulamaları. Caucasian Journal of Science,. 2020;7(1):28–41.
25. Güngörmüş Z, Kıyak E. Ağrı Yaşayan Bireylerin Tamamlayıcı ve Alternatif Tedaviye İlişkin Bilgi, Tutum ve Davranışlarının Değerlendirilmesi. Ağrı Dergisi,. 2012;24(3):123–129.
26. Erdoğan M. Genç Kızlarda Primer Dismenore ve Vücut Kitle İndeksi. (Yüksek Lisans Tezi) . Aydın: Adnan Menderes Üniversitesi, Sağlık Bilimleri Enstitüsü, Doğum-Kadın Sağlığı ve Hastalıkları Hemşireliği Anabilim Dalı, 2013.
27. Metin E, Kahyaoğlu Süt H. Genç Kadınlarda Primer Dismenore ile Antropometrik Ölçümler ve Vücut Kompozisyonları Arasındaki İlişki. Samsun Sağlık Bilimleri Dergisi,. 2021;6(2):317–330.
28. Zurawiecka M, Wronka I. Association of Primary Dysmenorrhea With Anthropometrical and Socio-Economic Factors in Polish University Students. Journal of Obstetrics and Gynaecology Research,. 2018;44(7):1259–1267.
29. Sönmezer E. Primer Dismenorede Konnektif Doku Masajı ve Kinezyobantlama Uygulamalarının Ağrı ve Yaşam Kalitesi Üzerine Etkilerinin Karşılaştırılması. (Doktora Tezi) . Ankara: Hacettepe Üniversitesi, Sağlık Bilimleri Enstitüsü, Fizik Tedavi ve Rehabilitasyon Programı, 2014.
30. Yılmaz T, Yazıcı S. Hemşirelik ve Ebelik Öğrencilerinin Dismenore Özellikleri. Anadolu Hemşirelik ve Sağlık Bilimleri Dergisi,. 2010;8–1.
31. Polat DC, Mucuk S. The Relationship Between Dysmenorrhea and Sleep Quality. Cukurova Medical Journal,. 2021;46(1):352–359.

32. Yılmaz T, Nuraliyeva Z, Dinç H. Genç Kadınların Dismenore ile Baş Etme Yöntemleri. JAREN,. 2020;6(2):294–299.
33. Yaşar Ö, Yıldırım D, Turhan S. Primer Dismenore ve Kişilik. Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi,. 2020;17(2):364–367.
34. Hailemeskel S, Demissie A, Assefa N. Primary Dysmenorrhea Magnitude, Associated Risk Factors, and İts Effect on Academic Performance: Evidence From Female University Students in Ethiopia. International Journal of Women's Health,. 2016;8:489–496.
35. Kuşaslan Avcı D, Sarı E. Üniversite Öğrencilerinde Dismenoreye Yaklaşım ve Dismenorenin Sosyal Yaşam ve Okul Performansına Etkisi. Van Tıp Dergisi,. 2018;25(2):188–193.
36. Yılmaz FA, Başer M. Dismenorenin Okul Performansına Etkisi. Gümüşhane Üniversitesi Sağlık Bilimleri Dergisi,. 2016;5(3):29–33.
37. Bakır N, Beji NK. Üniversite Öğrencilerinde Premenstrual Sendrom Prevelansı ve Etkileyen Faktörler. İnönü Üniversitesi Sağlık Hizmetleri Meslek Yüksek Okulu Dergisi,. 2021;9(1):264–277.
38. Topel M, Pehlivan M. Sağlık Bilimleri Fakültesinde Okuyan Kız Öğrencilerin Premenstrual Sendrom Yaşama Durumları ile Beslenme Alışkanlıklarının Değerlendirilmesi. KTO Karatay Üniversitesi Sağlık Bilimleri Dergisi,. 2021;2(3):84–96.
39. Dogan H, Demir Çaltekin M, Onat T, Aydoğan Kırmızı D, Başer E, Yalvaç ES. Approaches of Dealing With Primary Dysmenorrhea and Relationship Between Kinesiophobia and Pain Severity. Konuralp Medical Journal,. 2020;12(3):551–556.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Determination of Ghrelin Immunoreactivity in the Pancreas Tissue of Rats Supplied with Melatonin

Melatonin Uygulanan Ratların Pankreas Dokusunda Ghrelin İmmünoreaktivitesinin Belirlenmesi

Ayse Aydogan[1], Engin Yalmanci[2], Seher Koc Saltan[3], Sahin Aslan[3]

[1]Department of Histology and Embryology, Faculty of Veterinary Medicine, Necmettin Erbakan University, Konya;
[2]Prof. Dr. Fahrettin Kirzioglu Science and Art Center; 3Department of Histology and Embryology, Faculty of Veterinary Medicine, Kafkas University, Kars, Türkiye

ABSTRACT

Aim: *This study aimed to determine the histological effect of melatonin administration on the pancreas and the localization of ghrelin, secreted from the pancreas, using immunohistochemical techniques.*

Material and Method: *The study utilized 30 male Sprague Dawley rats aged 10–12 weeks. Melatonin was dissolved in ethanol and injected intraperitoneally into the experimental group at 10 mg/kg for 21 days, diluted with a physiological saline solution. After the experimental period, pancreatic tissues were collected from the rats. These tissue samples were fixed in 10% formalin for histological and immunohistochemical examinations and underwent routine histological procedures. The tissues were then treated with a ghrelin antibody (diluted to 1/50) to determine the immunohistochemical localization of ghrelin.*

Results: *Upon examination of the general histological structure of the pancreatic tissue, no differences were observed between the groups. Ghrelin immunoreactivity was detected in the islets of Langerhans and the pars initialis epithelium of the pancreas in both the sham and control groups but not in the melatonin group.*

Conclusion: *Melatonin administration did not induce any histological disorders in the pancreas. However, it was found to decrease the ghrelin levels secreted from the pancreas.*

Key words: *ghrelin; immunohistochemistry; melatonin; pancreas*

ÖZET

Amaç: *Melatonin uygulamasının, pankreas üzerindeki histolojik etkisi ve pankreastan sekresyonu sağlanan ghrelinin, immünohistokimyasal olarak lokalizasyonunun belirlenmesi amaçlanmıştır.*

Materyal ve Metot: *Çalışmada 10–12 haftalık 30 adet erkek Spraque Dawley türü rat kullanıldı. Melatonin, etanolde çözdürülüp serum fizyolojik su ile sulandırılarak 10 mg/kg dozda ve 21 gün boyunca intraperitoneal yolla deneme grubuna enjekte edildi. Deneysel uygulamanın sonunda ratların pankreas dokuları alındı. Histolojik ve immünohistokimyasal incelemelerde kullanılmak üzere pankreas doku örnekleri %10'luk formalde tespit edilerek rutin histolojik işlemlerden geçirildi. Ghrelinin immünohistokimyasal lokalizasyonunu belirlemek amacıyla, dokulara ghrelin antikoru (1/50 dilüsyonunda) uygulandı.*

Bulgular: *Pankreas dokusunun genel histolojik yapısı incelendiğinde, gruplar arasında bir farklılık olmadığı tespit edildi. Sham ve kontrol gruplarında ghrelin immünoreaktivitesi pankreasın, Langerhans adacıklarında ve pars inisiyalis epitelinde görüldü. Melatonin grubunda ise immünoreaktivite görülmedi.*

Sonuç: *Melatonin uygulamasının, pankreasta herhangi bir histolojik bozukluğa yol açmadığı görüldü. Melatonin uygulamasının pankreastan salgılanan ghrelin seviyesini düşürdüğü tespit edildi.*

Anahtar kelimeler: *ghrelin, immünohistokimya, melatonin, pankreas*

Introduction

Melatonin is a hormone synthesized and secreted from the pineal gland located between the cerebral hemispheres, bone marrow cells, lens, ovary, gastrointestinal system, and bile in the brain of mammals[1,2]. Melatonin does not show a homogeneous distribution in the gastrointestinal tract and is present in different concentrations and parts. Gastrointestinal tract melatonin is entirely related to serotonin concentration, which supports the idea that melatonin production in the gastrointestinal tract is independent of the pineal gland. It is known that the gastrointestinal tract melatonin level is not affected by pinealectomy[3,4]. Literature on the pancreas indicates that melatonin has a protective effect on this organ[5].

İletişim/Contact: *Ayse Aydogan, Department of Histology and Embryology, Faculty of Veterinary Medicine, Necmettin Erbakan University, Konya, Türkiye* • ***Tel:*** *0536 675 79 84* • ***E-mail:*** *aydoganayse12@gmail.com* • ***Geliş/Received:*** *12.07.2023* • ***Kabul/Accepted:*** *16.02.2024*

ORCID: *Ayşe Aydoğan: 0000-0001-7317-6486 • Engin Yalmancı: 0000-0001-9416-3158 • Seher Koç Saltan: 0000-0003-3795-5145 • Şahin Aslan: 0000-0002-4565-9832*

Kafkas J Med Sci 2024; 14(1):48–53
doi: 10.5505/kjms.2024.98957

It is known that ghrelin, which can secrete growth hormone from the stomach of rats, was detected in 1999[6]. It is known that ghrelin is derived from the word 'ghre', which means 'to grow' in Proto-Indo-European languages[7]. The ghrelin is a hormone found in mammals and other vertebrate species such as chickens, frogs, and fish, and a delicious peptide hormone consisting of 28 amino acids[7,8]. The ghrelin has two different molecular forms. These are acyl ghrelin of 28 amino acids (modified form) and des-acyl ghrelin of 27 amino acids (unmodified form)[9,10]. Acyl ghrelin forms one-fifth of the ghrelin immunoreactivity in rat stomach[11]. In the gastrointestinal system, ghrelin has stimulating effects on the motility of the digestive tract during satiety and hunger[10].

Ghrelin is primarily produced in the stomach, particularly in the densest areas[12,7]. Additionally, it is produced in various other locations within the body, including the hypothalamus, brain, pituitary gland, adipose tissue, heart, lungs, and pancreas[7,13,14].

The literature has documented that the pancreas is an organ that produces ghrelin. It is known that the pancreatic cells responsible for ghrelin secretion are α and β cells[15,16]. In the postnatal period, the pancreatic ghrelin-expressing cells are high in number (around 10% of all endocrine cells)[17]. The ghrelin mRNA and protein are known to be found in the pancreas. These proteins are expressed in α[16] and β[15] cells of the pancreas. Several studies show that ghrelin upregulates insulin production in the pancreas[18,19]. It is also known to reduce plasma glucose levels in humans[20].

The study aims to determine the histological effect of melatonin administration on the pancreas and the localization of ghrelin, of which secretion is provided from the pancreas immunohistochemically.

Materials and Methods

Ethical approval of the study was obtained from the Animal Experiments Local Ethics Committee of Kafkas University (Date: 25.05.2022, Decision No: 107 and Research Code: KAU-HADYEK/2022-107). All stages of the study were conducted in the Department of Histology and Embryology Laboratory, Faculty of Veterinary Medicine, Kafkas University.

Experimental Animal Material: The experimental animals used in the study were obtained from the Erzurum Veterinary Control Institute. Thirty male *Spraque Dawley* rats, which were 10–12 weeks old, were used in the study. During the experiment, the subjects were fed rat chow as *adlibitum*. After a 15-day adaptation period, the subjects were divided into three groups: the experimental group, the sham group, and the control group. The subjects were housed in standard cages with a 12-hour light-dark cycle and a room temperature of 22±2°C.

Experimental Groups: The study included three experimental groups (control, sham, and melatonin). Melatonin (Sigma-M5250), stored at -20°C, was brought to the laboratory under cold chain conditions. Melatonin, dissolved in ethanol and diluted with physiological saline water at a dose of 10 mg/kg, was administered to the experimental group intraperitoneally for 21 days (in the evening hours). The sham group received injections of the same volume of ethanol and saline water as the experimental group for 21 days. No administration was made to the control group. A total of 30 rats were used, with 10 subjects in each group.

Removal of Pancreatic Tissues: At the end of the 21-day experimental period, the subjects were euthanized under anesthesia, and their pancreatic tissues were removed. The pancreatic tissue samples were fixed in 10% formalin for histological and immunohistochemical examinations.

Histological Studies: 5 μm thick sections were taken from the paraffin-blocked tissues on the slides coated with chrome alum gelatin. Crossman's Triple Staining was performed on tissue sections to examine the histological structure of the pancreas.

Immunohistochemical Studies: 5 μm thick sections were taken from the blocked tissues to examine the immunohistochemical localization of ghrelin in the pancreatic tissue. Deparaffinization and dehydration processes were applied to the prepared sections. It was washed in phosphate-buffered saline (PBS) and incubated for 15 minutes in 3% H_2O_2 prepared in 0.1 M PBS. After the sections were rewashed with PBS, 600 watts of heat were applied to the citrate buffer in a microwave oven for 10 minutes. It was rewashed with PBS and incubated for 10 minutes in UV serum (10%), suitable for the secondary antibody to prevent non-specific bindings. After washing with PBS again, the anti-ghrelin antibody (Phonex H-031-31, at 1:50 dilution ratio) was administered to the sections and incubated for 24 hours at room temperature. At the end of the period, the biotinylated secondary antibody was administered to the tissues that were rewashed with

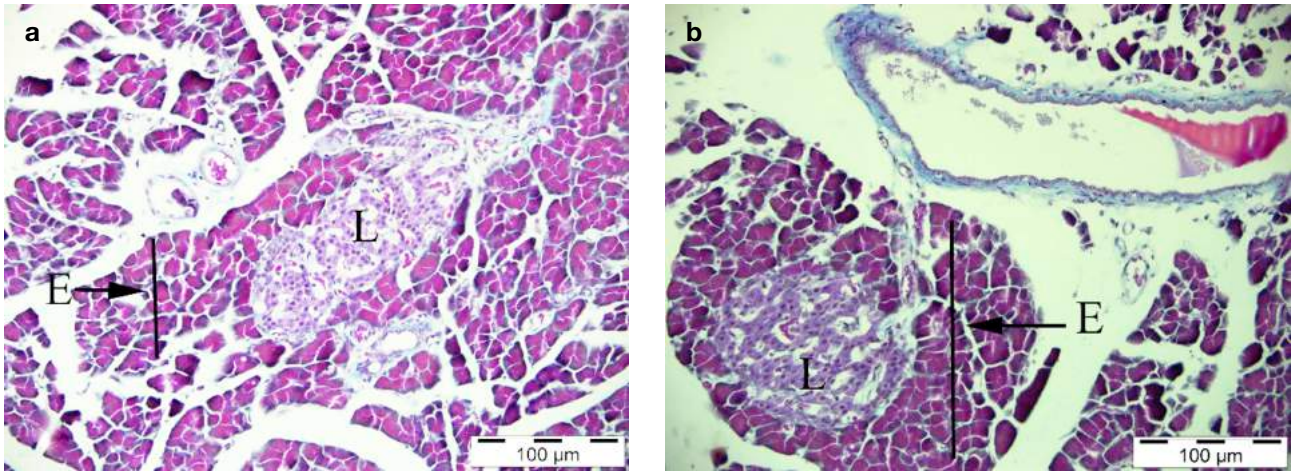

Figure 1. *a, b. Pancreas image with melatonin application (a). Pancreas image of the control group (b) (E: Exocrin pancreas, L: Islets of Langerhans, Triple staining).*

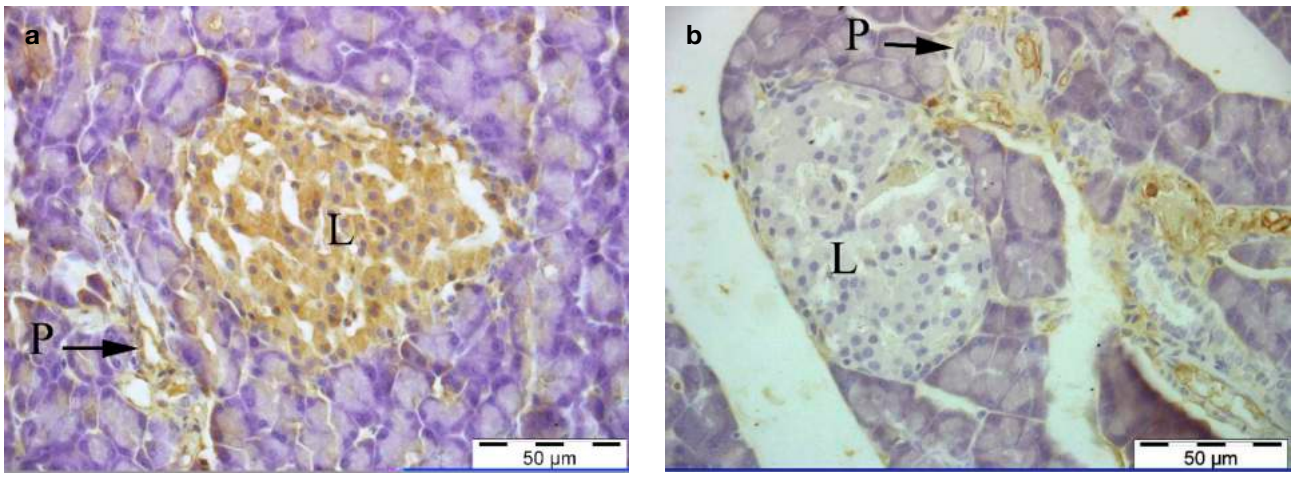

Figure 2. *a, b. Ghrelin immunoreactivity of the control group (a). Ghrelin immunoreactivity of the Melatonin group (b) (L: Islets of Langerhans, P: Pars initialis).*

PBS and left at room temperature for 30 minutes. After the repeated washing process, the sections were incubated for 30 minutes by administering streptavidin peroxidase. After washing with PBS again, chromogen was administered diaminobenzidine (DAB (Thermo TA-125-HD)). After administering chromogen solution to the sections, the reaction was stopped with distilled water in a controlled manner according to the formation of immunoreactivity. As a result of the dehydration and clearing processes by administering hematoxylin as a counter dye to the prepared tissues, the sections were closed with a coverslip with the help of entellan.

The prepared slides were examined under a light microscope and photographed. The density grades of cells with immunoreactivity were determined.

All steps were administered similarly, except for administering the ghrelin antibody to the negative control to determine the specificity of tissue ghrelin immunoreactivity.

Results

Histological Findings: The tissue samples from all three groups (melatonin, sham and control) were treated with triple staining to examine the pancreatic tissue's general histological structure. According to the evaluations, it was determined that the administration of melatonin did not cause any damage to the tissues, and the melatonin group and sham group pancreatic tissues were similar to the control group. It was observed that the structures in the endocrine and exocrine parts of the pancreas were normal in all groups (Fig. 1).

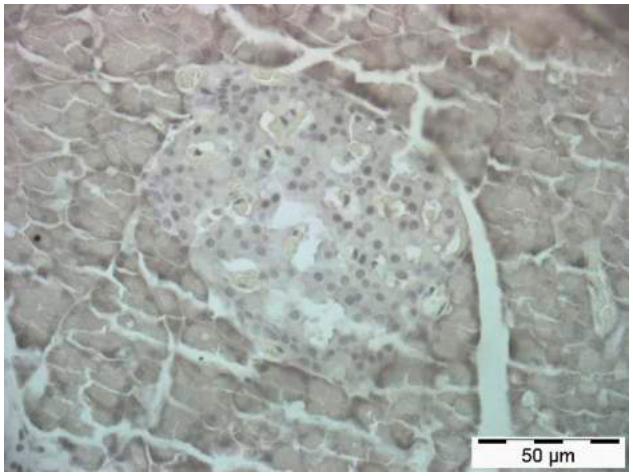

Figure 3. *Negative control of the ghrelin immunoreactivity in the pancreatic tissue.*

Immunohistochemical Findings: In our study, the ghrelin expression was examined immunohistochemically in the experimental, sham, and control groups. According to the evaluations, the immune reaction was observed in the islets of Langerhans, connective tissue areas, and pars initialis epithelium of the pancreatic sections in the control group. In the melatonin group, the ghrelin immunoreactivity was positive in the islets of Langerhans, connective tissue areas, and pars initialis epithelium of the pancreas. However, the immunoreactivity in the melatonin group was found to be weaker than in the control group. The immunohistochemical findings show that the melatonin administration suppresses the ghrelin expression (Fig. 2). It was observed that there was no immunoreaction in the negative staining of ghrelin (Fig. 3).

Discussion

It was determined that melatonin increased the activities or gene expressions of some antioxidant enzymes such as superoxide dismutase, glutathione reductase, and glutathione peroxidase and suppressed oxidative stress in this way[2]. In the oxidative damage induced by paraquat, melatonin was reported to reduce the level of lipid peroxidation product in rats[21]. According to the study of Akçay[22] (2017), melatonin administration prevents damage by increasing the antioxidant level in the gastrointestinal tract. It has a protective effect on the digestive tract canal. Yuzüak[23] (2014) reported that melatonin is a potent radical scavenger; it has an antidamage impact on the pancreas and thus protects the pancreatic tissue. The study of Javorek et al.[24] (2012) stated that the melatonin administration made to the rats exposed to acute pancreatitis and pineal gland removal by pinealectomy significantly reduced the lesions formed in the pancreatic tissue.

In our study, it was determined that the administration of melatonin did not cause any histological disorder in the pancreatic tissue of the rats, and the pancreas images obtained in all groups were in accordance (Ross and Pawlina 2011)[25].

Bianchini et al.[26] (2012) reported that ghrelin immunoreactivity was found in the duodenal epithelium in the sleeve gastrectomy they made in Wistar rats. In a study conducted by Akbalik[27] (2019), the ghrelin immunoreactivity in the gastrointestinal system of Partridge (Alectoris chukar) was in the epithelial layer of the digestive tract. In many studies conducted in rats, it was reported that there was a strong ghrelin immunoreaction in the alveolar and duct epithelial cells of the mammary tissue[28,29]. A study conducted by Tanaka et al.[30] (2005) reported that the ghrelin immunoreactivity was intense in the lamina muscularis layer of the human stomach.

The immunoreactivity of ghrelin in pancreatic tissue was evaluated in many organisms. Some of these studies are in humans, rats[15], mice, fish, birds[31], chickens[32], geese[33], and frogs[34]. According to the results of immunohistochemistry performed by Raghay et al.[35] (2013) in rat pancreas, it was reported that ghrelin immunoreactivity was found in islet cells in the center of the pancreas. According to the immunohistochemical study conducted by Wang et al.[31] (2017) in the pancreas of African ostrich chicks (Struthio camelus), they stated that the immunoreactivity of ghrelin was positive in both pancreatic islets and acinar cell regions. It was determined that the reaction was most intense in the islets of Langerhans and the areas close to it. Wang et al.[31] (2017) stated that the ghrelin immunoreactivity was also found in the ducts of the exocrine pancreas. In a study conducted on rats, Sönmez[36] (2017) reported that melatonin had a suppressive effect on the level of ghrelin in the serum.

Our study evaluated the ghrelin immunoreactivity in the pancreatic tissue of rats treated with tonin. It was determined that the findings obtained were under the studies carried out. In the control group, the immune reaction was detected in the islets of Langerhans, connective tissue areas, and pars initialis epithelium of the pancreatic sections. In the melatonin group, it was determined that the ghrelin immunoreactivity was positive in the islets of Langerhans, connective tissue areas,

and pars initialis epithelium of the pancreas. Still, the immunoreactivity in the melatonin group was weaker than in the control group. Our findings were observed to be parallel with Sönmez's[36] (2017) data, which showed that the melatonin administration suppressed the ghrelin expression.

Melatonin administration suppresses oxidative stress by increasing antioxidant enzyme activities and gene expressions. It is also known that increasing the antioxidant level prevents damage to various tissues of the organism. It was observed that melatonin administration did not cause histological deterioration in the pancreatic tissue. It was determined that the ghrelin immunoreactivity was suppressed. The ghrelin triggers insulin release in the pancreas. It is also known to lower the plasma glucose level. Therefore, we think more detailed studies should be done on this subject.

Conflict of Interest

The authors declare no conflict of interest regarding the publication of this manuscript.

References

1. Liebmann PM, Wölfler A, Felsner P, Hofer D, Schauenstein K. Melatonin and the immune system. İnt. Arch. Allergy. İmmunol. 1997;112:203–211.
2. Reiter RJ, Tan D, Osuna C, Gitto E. Actions of melatonin in the reduction of oxidative stress. J. Biomed Sci. 2000;7:444–458.
3. Konturek SJ, Konturek PC, Brzozowska I, Pawlik M, Sliwowski Z, Czesnikiewicz-Guzik M, et al. Localization and biological activities of melatonin in intact and diseased gastrointestinal tract (GIT). J Physiol Pharmacol. 2007;58:381–405.
4. Bubenik GA. Localization, physiological significance and possible clinical implication of gastrointestinal melatonin. Biol Signals Recept. 2001;10:350–366.
5. Ebelt H, Peschke D, Bromme HJ, Morke W, Blume R, Peschke E. Influence of melatonin on free radicalinduced changes in rat pancreatic beta-cells in vitro. J Pineal Res. 2000;28:65–72.
6. Kojima M, Hosada H, Date Y. Ghrelin is a growth hormone releasing acylated peptide from stomach. Nature. 1999;402:656–660.
7. Kukol A. Ghrelin Vitamins and Hormon, The Structure of Ghrelin. 2008;77–79.
8. Kojima M, Kangawa K. Ghrelin: structure and function. Physiol. 2005;85:495–522.
9. Ariyasu H, Takaya K, Tagami T, Ogawa Y, Hosoda K, Akamizu T, et al. Stomach is a major source of circulating ghrelin, and feding state determines plasma ghrelin-like immunoreactivity levels in humans. J Clin Endocrinol Metab. 2001;86:4753–4758.
10. Fujimiya M, Asakawa A, Ataka K, Chen CY, Kato I, Inui A. Ghrelin, des-acyl ghrelin, and obestatin: regulatory roles on the gastrointestinal motility. Int J Pept. 2010;
11. Hosoda H, Kojima M, Matsuo H, Kangawa K. Purification and characterization of rat desGln14-Ghrelin, a second endogenous ligand for the growth hormone secretagogue receptor. J Biol Chem. 2000;275:21995–2000.
12. Sakata I, Nakamura K, Yamazaki M, Matsubara M, Hayashi Y, Kangawa K, et al. Ghrelin-producing cells exist as two types of cells, closed- and opened-type cells, in the rat gastrointestinal tract. Peptides. 2002;23:531–536.
13. Cowley M, Smith R, Diano, Tschop M, Pronchuk N, Stasburger C, et al. The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis. Neuron. 2003;37:649–661.
14. Korbonits M, Bustin SA, Kojima M, Jordan S, Adams EF, Lowe DG, et al. The expression of the growth hormone secretagogue receptor ligand ghrelin in normal and abnormal human pituitary and other neuroendocrine tumors. J Clin Endocrinol Metab. 2001;86:881–887.
15. Date Y, Kojima M, Hosoda H, Sawaguchi A, Mondal MS, Suganuma T, et al. Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. Endocrinology. 2000;141:4255–4261.
16. Volante M, Allia E, Gugliotta P, Funaro A, Broglio F, Deghenghi R, et al. Expression of ghrelin and of the GH secretagogue receptor by pancreatic islet cells and related endocrine tumors. J Clin Endocrinol Metab. 2002;87:1300–1308.
17. Chanoine JP, Wong AC. Ghrelin gene expression is markedly higher in fetal pancreas compared with fetal stomach: effect of maternal fasting. Endocrinology. 2004;145:3813–3820.
18. Adeghate E, Ponery AS. Ghrelin stimulates insulin secretion from the pancreas of normal and diabetic rats. Journal of neuroendocrinology. 2002;14(7):555–560.
19. Lee HM, Wang G, Englander EW, Kojima M, Greeley GH. Ghrelin, a new gastrointestinal endocrine peptide that stimulates insulin secretion: enteric distribution, ontogeny, influence of endocrine, and dietary manipulations. Endocrinology. 2002;143(1):185–190.
20. Broglio F, Arvat E, Benso A, Gottero C, Muccioli G, Papotti M, et al. Ghrelin, a natural GH secretagogue produced by the stomach, induces hyperglycemia and reduces insulin secretion in humans. The Journal of Clinical Endocrinology & Metabolism. 2000;86(10):5083–5083.
21. Melchiorri D, Reiter RJ, Attia AM. Potent protective effect of melatonin on in vivo paraquat-induced oxidative damage in rats, Life Sci. 1994;56:83–89.
22. Akçay GB. Stretozotosin İle Diyabet Oluşturulan Sıçanlarda Bağırsak Dokusunda Gelişen Oksidan Hasara Karşı Melatonin Tedavisinin Olası Koruyucu Etkilerinin İncelenmesi, Marmara Üni., Sağlık Bilimleri Enstitüsü, Farmakoloji Anabilim Dalı, İstanbul, 2017.

23. Yüzüak H. Melatoninin streptozotosin kaynaklı deneysel diyabet üzerine olası koruyucu etkisi. Klinik ve Deneysel Araştırmalar Dergisi. 2014;5(4):592–598.
24. Jaworek J, Szklarczyk J, Jaworek AK, Nawrot-Porąbka K, Leja-Szpak A, Bonior J, et al. Protective Effect of Melatonin on Acute Pancreatitis. International Journal of Inflammation. 2012;1–8.
25. Ross H, Wojciech Pawlina. Histology A Text and Atlas, Histoloji. ISBN 978–0–7817–7200–6, 2011.
26. Bianchini M, Fantazzinni TR, Vieira DSC, Teive AM, Costa A. Quantitative immunohistochemical analysis of duodenal ghrelin cells after sleeve gastrectomy in Wistar rats, Acta Cirurgica Brasileira. 2012;27(9):535 599.
27. Akbalık ME. Keklik (Alectoris chukar) Bağırsağında Ghrelin, Leptin ve Obestatin Dağılımı. Dicle Üniv Vet Fak Derg. 2019;12(2):117–121.
28. Grönberg, M, Tsolakis AV, Magnusson, L, Janson ET, Saras J. İnsan Dokularında Obestatin ve Ghrelin Dağılımı. Histokimya ve Sitokimya Dergisi. 2008;56(9);793–801.
29. Zhang W, Zhang Z, Chen J, Tong D. Ghrelin is Expressed in the Pregnant Mammary Glands of Dairy Goats and Promotes the Cell Proliferation of Mammary Epithelial Cells. Gen Comp Endocrinol. 2018;260:115–124.
30. Tanaka-Shintani M, Watanabe M. Distribution of ghrelin-immunoreactive cells in human gastric mucosa: comparison with that of parietal cells. J Gastroenterol. 2005;40:345–349.
31. Wang J, Li P, Zhang XT. Distribution and developmental changes of ghrelin-immunopositive cells in the pancreas of African ostrich chicks (Struthio camelus) . Poultry science. 2017;96(9):3445–3451. PMID:28595319.
32. Wei FM, Li YL, Ye Y, Zhang YJ, Jiang QY. Localization and development of ghrelin-immunopositive cells in periphery organs of broiler chickens. Acta Vet. Zootech. Sin. 2010;41:341–346.
33. Fang FG, Li MQ, Tao Y, Jiang SD, Li FB. Immunohistochemical localization of ghrelin in the liver and pancreas of adult Wanxi white goose. Chin. J. Anat. 2008;31:28–30.
34. Suzuki H, Yamamoto T. Ghrelin-and growth hormone secretagogue receptor- immunoreactive cells in Xenopus pancreas. Regul. Pept. 2011;169:64–69.
35. Raghay K, Gallego R, Scoazec JY, Garcia-Caballero T, Morel G. Different ghrelin localisation in adult human and rat endocrine pancreas. Cell Tissue Res. 2013;352:487–494.
36. Sönmez S. Sıçanlarda Pinealektomi ve Melatonin Uygulamasının Serum Melatonin, Nesfatin-1 ve Ghrelin Düzeylerine Etkisi. Selçuk Üni. Sağlık Bilimleri Enstitüsü, Yüksek Lisans Tezi, Konya, 2017.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Empirical Research Investigating the Relationships Between Work Stress, Work Performance, and Mobbing (Psychological Bullying) in Health Institutions

Sağlık Kurumlarında İş Stresi, Çalışan Performansı ve Mobbing (Psikolojik Yıldırma) Arasındaki İlişkilerin İncelenmesine Yönelik Ampirik Araştırma

Gokhan Keles[1], Caglar Dogru[1], Ayse Ikinci Keles[2]

[1]Department of Management and Organization, Ufuk University, Ankara, Türkiye
[2]Department of Histology and Embryology, Faculty of Medicine, Aksaray University, Aksaray, Türkiye

ABSTRACT

Aim: *This study examines the relationships between work stress, work performance, and mobbing in health institutions.*

Material and Method: *A questionnaire was applied to 272 individuals working in any health institution in Türkiye in 2021 based on voluntary participation with the snowball method. The web-based questionnaires were prepared online using Google Documents. They were sent to the health workers' social-based addresses together with an introductory letter. The questionnaire was applied in four main sections: demographic information (8 questions), work stress (7 questions), work performance (4 questions), and mobbing (37 questions).*

Results: *The study showed that 36.4% of academics, 30% of secretaries, 28.6% of security staff, 23% of technicians, 22.2% of social workers, 20% of midwives, 19.5% of physicians, and 15.4% of patient carers were exposed to mobbing. In addition, men were more subjected to mobbing than women (p=0.010). Statistically significant differences were determined between the occupational groups regarding work stress scale scores (p=0.001). The group with the highest work stress was security staff, with patient carers being the group with the lowest stress. Women also experienced significantly higher levels of work stress than men (p=0.028). Statistically, significant differences were also observed regarding the number of patients encountered (p=0.035). Work stress was found to increase in line with patient numbers. Analysis of the participants' work performance showed that such performance was very high. Significant variations were determined between work performance scale scores and the years spent working in the most recent institution (p=0.019). The work performance of participants who had worked for 11–15 years was lower than that of other periods, the highest work performance being observed in participants with 21–25 years of work experience.*

Conclusion: *In conclusion, individuals working in any health institution were found to be exposed to mobbing and to experience work stress in the working environment but exhibited good work performance. No statistically significant association was determined between mobbing and work performance or stress. At the same time, a negative correlation was observed between work performance and work stress.*

Key words: *health institution; work performance; mobbing; Türkiye, work stress*

ÖZET

Amaç: *Bu çalışmanın amacı sağlık kurumlarında iş stresi, iş performansı ve mobbing arasındaki ilişkileri incelemektir.*

Materyal ve Metot: *2021 yılında Türkiye'deki herhangi bir sağlık kuruluşunda çalışan 272 bireye, gönüllü katılım ilkesine dayalı olarak, kartopu yöntemiyle anket uygulandı. Web tabanlı anketler Google Documents kullanılarak çevrimiçi olarak hazırlanmış ve tanıtım yazısı ile birlikte sağlık çalışanlarının sosyal adreslerine gönderilmiştir. Anket, demografik bilgiler (8 soru), iş stresi (7 soru), iş performansı (4 soru) ve mobbing (37 soru) olmak üzere dört ana bölümde uygulanmıştır.*

Bulgular: *Çalışmanın sonucuna göre, akademisyenlerin %36,4, sekreterlerin %30, güvenliklerin %28,6, teknikerlerin %23, sosyal hizmetlerin %22,2, hemşirelerin %20,2, ebelerin %20, hekimlerin %19,5, hasta bakıcıların %15,4 oranında mobbinge maruz kaldığı tespit edilmiştir. Ayrıca erkeklerin kadınlara göre daha fazla mobbinge maruz kaldıkları sonucu elde edilmiştir (p=0,010). Meslek grupları arasında iş stresi ölçeği puanları açısından istatistiksel olarak anlamlı farklılıklar belirlendi (p=0,001). İş stresinin en yüksek olduğu grup güvenlik personeli olurken, en düşük iş stresinin yaşandığı grup ise hasta bakıcıları oldu. Ayrıca kadınların iş stresinin erkeklere göre daha fazla (p=0,028) olduğu ve kişilerin karşılaştıkları hasta sayıları arasında (p=0,035) istatistiksel olarak farklılıklar bulunmuştur. Hasta sayısı arttıkça iş stresinin arttığı tespit edilmiştir. Katılımcıların iş performansları sonucuna göre katılımcılarda çalışma performansının çok yüksek olduğu tespit edilmiştir. Katılımcılara uygulanan iş performansı ölçek puanı ile katılımcıların en son çalıştıkları kurumdaki toplam çalışma yılı karşılaştırıldığında istatistiksel olarak farklılıklar bulunmuştur (p=0,019). Buna göre 11–15 yıl arasında çalışanların performanslarının diğer çalışma yıllarına göre düşük olduğu, 21–25 yıl arasında çalışanlarda ise performansın en yüksek olduğu tespit edilmiştir.*

Sonuç: *Sonuç olarak, herhangi bir sağlık kuruluşunda çalışan bireylerin çalışma ortamında mobbinge maruz kaldıkları ve iş stresi yaşadıkları ancak buna rağmen iyi iş performansı sergiledikleri belirlendi. Mobbing ile iş performansı veya iş stresi arasında istatistiksel olarak anlamlı bir ilişki saptanmazken, iş performansı ile iş stresi arasında negatif bir ilişki gözlendi.*

Anahtar kelimeler: *iş performansı, iş stresi, mobbing, Türkiye, sağlık kurumu*

İletişim/Contact: *Ayse Ikinci Keles, Department of Histology and Embryology, Faculty of Medicine, Aksaray University, Aksaray, Türkiye* •
Tel: *0536 665 12 52* • ***E-mail:*** *ayse_ikinci@hotmail.com; ayseikincikeles@aksaray.edu.tr* • ***Geliş/Received:*** *06.09.2023* • ***Kabul/Accepted:*** *20.01.2024*

ORCID: *Ayse İkinci Keleş: 0000-0003-0716-5695 • Çağlar Doğru: 0000-0002-4215-8979 • Gökhan Keleş: 0000-0002-4875-9820*

Introduction

Mobbing (psychological bullying) has been described as hostile or unethical communication directed against a single individual by one or more persons[1]. These behaviors assume two forms – top-down or bottom-up (hierarchical) and horizontal mobbing. Irrespective of the particular form, the outcomes of mobbing are always poor. The effects of mobbing can be seen in all stages of society (in working and societal life), and the number of studies investigating these effects is increasing rapidly[2]. Nobody's freedom can be restricted, irrespective of which section of society they belong to.

Performance evaluation is one of the responsibilities of human resource management. Performance appraisal must not go beyond its objective. The institutions studied must determine specific methods and rules for evaluations. All factors obstructing performance evaluation during appraisals must be eliminated, and assessments must be unbiased, clear, and transparent[3].

Membership in an organization is not solely limited to productivity. At the same time, individuals must establish communication, adapt to the environment, and forge links, which results in stress. Stress is defined as an occult structure that shows a high state of activation of the autonomous nervous system emerging in coordination at the emotional, cognitive, and behavioral levels[4]. Individual, societal, and organizational sources are essential regarding the causes of stress. Work stress can result in very severe consequences. These include adverse impacts on health (such as cardiovascular diseases, metabolic disorders, or depression)[5] and can also manifest in burnout and exhaustion. Increased work stress can even result in staff losses. Various individual and organizational measures can be adopted in the face of work stress. Organizational stress will also develop due to performance evaluations in the workplace, as described above. Exposure to mobbing in the workplace will further exacerbate this stress.

In our study, a model was applied to determine the relationships between job stress, job performance, and mobbing, and the questionnaires were filled out by individuals working in a health institution. In this model, the work stress, job performance, and mobbing results of individuals in health institutions will be evaluated first. Then, the relationships between job stress, job performance, and mobbing will be revealed according to the results. Our study is based on three hypotheses. Our first hypothesis is that there is a statistically significant and negative linear relationship between mobbing and work stress. Our second hypothesis is that there is a statistically significant and negative linear relationship between mobbing and job performance. Our third hypothesis is that there is a statistically significant and negative linear relationship between job performance and job stress.

Performance evaluation, exposure to mobbing, and work stress among health workers affect the working environment. Despite being distinct, each can result in or originate from the others. Exposure to mobbing can exacerbate work stress and affect performance. Low performance can also exacerbate work stress. All these situations manifestly impact the work sphere. Each one must, therefore, be considered individually, and its effects on workers must be noticed. In light of all these factors, the present study was intended to examine the relationships between work stress, worker performance, and mobbing among individuals working in health institutions in Türkiye.

Method

Ethical Issues

The study commenced following receipt of approval from the Niğde Ömer Halisdemir University Non-Interventional Research Ethical Committee (no. 2020/65 dated 14.01.2021). Electronic informed consent was obtained from all participants, and the research was conducted in conformity with the principles of the Declaration of Helsinki.

Procedures

Participants

In 2021, this observational, cross-sectional study was performed among health workers living in seven regions of Türkiye (Marmara, the Aegean, the Black Sea, Central Anatolia, the Mediterranean, and Southeast Anatolia). Two hundred seventy-five individuals meeting the inclusion criteria responded to the study questions. However, three participants were excluded for making the 'no' box in response to the statement, 'I am participating in this research of my own free will and consent to the information provided by me being used in scientific research.' The study sample size was 272. The snowball method employed in the research is a non-probability-based sampling method. The population in such studies cannot, therefore, be defined[6].

Research Acceptance Criteria

Inclusion criteria were established to identify individuals suitable for inclusion in the research:

a) Willingness to take part in the study, b) Working in a health institution, and c) Having been employed in the present institution for at least six months. Being employed in an institution for at least six months is a precondition for a behavior to be regarded as mobbing[1].

Data Collection

Questionnaires were administered to collect data from individuals working in any health institution in Türkiye. The questionnaires were applied based on voluntary participation, and the 'snowball sampling' method was employed[7]. This method is mainly employed in research into sensitive subjects (such as addictions, child abuse, or rape). Such individuals are often reluctant to share their experiences, but this problem can be easily overcome using this method[8]. In addition, due to this sensitivity, no information concerning the identity of the participants of the institutions in which they worked was included in the questions posed.

The data were collected from a questionnaire created by the researchers using an online questionnaire between 01 February 2021 and 20 February 2021. The web-based questionnaires were prepared online using Google Documents. They were sent to the health workers' social-based addresses (e-mail, Whatsapp, Instagram, Facebook, etc.) with an introductory letter. Web-based consent was obtained from the individuals taking part. The questionnaire was applied in four main sections.

Section one – demographic information (eight questions): The questions in this section concerned age, marital status, education, total number of years worked in the current institution, occupation, and mean daily numbers of patients cared for.

Section two – the work stress scale (seven questions): The Work Stress Scale developed by House and Rizzo in 1972 was employed[9]. This scale was adapted into Turkish by Efeoğlu in 2006, and its validity and reliability have been proved in studies in which it was used[10].

Section three – work performance scale (four questions): The scales employed in the Kirkman and Rosen[11] study, and subsequently by Sigler and Pearson[12], were applied. The scale was adapted into Turkish by Çöl in 2008, and its validity and reliability have been demonstrated[13].

Section four – mobbing scale (37 questions): The Mobbing Scale in the fourth section was developed by Aiello et al.[14]. The scale was adapted into Turkish by Laleoğlu and Özmete in 2013, and its validity and reliability were confirmed[15]. The test contains 37 questions. These investigate differing characteristics, meaning the scale is divided into separate sections. Five factors appear in the Mobbing Scale (relations with colleagues, 16 questions; threat and harassment, seven questions; job and career, eight questions; intervention in private life, four questions; and commitment to work, two questions)[15].

A five-point Likert-type scale was employed for the work stress, mobbing, and performance questions in the rankings: 1- strongly disagree, 2- disagree, 3- undecided, 4- agree, and 5- strongly agree. Strongly disagree responses are scored 1, Disagree 2, Undecided 3, Agree 4, and Strongly Agree 5. The lowest possible score for work stress was seven, and the highest was 35. The mobbing lowest possible score was 37, and the highest was 259. The performance's lowest possible score was 4, and the highest was 20.

The Research Model

The model applied in the present study was intended to determine relationships between work stress, work performance, and mobbing using a questionnaire completed by individuals working in health institutions. The work stress, work performance, and mobbing results for the individuals working in health institutions were first evaluated in this model. Relationships between work stress, work performance, and mobbing were then investigated.

Statistical Analysis

Statistical analysis of the study data was performed on IBM Statistical Package for Social Sciences (SPSS) program version 22 software (IBM Inc., USA). The normality of distribution was examined using the Kolmogorov-Smirnov test. Cronbach Alpha, T-test, One-Way ANOVA, and chi-square tests were employed in the analysis. Data were expressed as mean ± standard deviation. p values <0.05 were regarded as significant for all comparisons.

Results

Reliability Analyses of the Scales Employed in the Research

Cronbach's Alpha, a coefficient of internal consistency, was calculated to determine the reliability of the work stress, work performance, and mobbing scales administered in the research[15]. Cronbach Alpha values of 0.90 for Work Stress, 0.82 for Work Performance, and 0.97 for Mobbing were determined. These results indicated that the scales employed exhibited high validity and reliability (values $0.81<\alpha<1.00$ indicate high scale reliability[16].

Demographic Results

Demographic data include sex, age, marital status, education, occupation, years worked in the current institution, and number of patients encountered daily. Examination of the participants' (272 individuals) responses showed that women (74.6%) outnumbered men (25.4%) and that married individuals (63.6%) outnumbered the unmarried (36.4). Regarding education, the minor participants were those educated to the primary level (0.7%), and the highest consisted of those educated to the university level (61.8%). The youngest participant was 20, and the oldest 65, with a mean age of 35.64±8.86. Men ages were 34.99±8.40 for women and 37.58±9.90 for men. In terms of the 18 occupational groups identified, nurses represented 36.4% of the individuals taking part in the study, physicians 15.1%, technicians 14.3%, patient carers 4.8%, academics 4.0%, midwives 3.7%, secretaries 3.7%, social workers 3.3%, data preparation staff 2.9%, security staff 2.6%, psychologists 1.8%, administrative personnel 1.5%, engineers 1.5%, pharmacists 1.5%, embryologists 1.1%, biologists 0.7%, physiotherapists 0.4%, and computer programmers 0.4%. The shortest time worked in the most recent institution was 0.5 years, and the longest was 32 years. The mean working time in the current institution was 10.12±8.55 years (Table 1).

Table 1. *Statistical data concerning Demographic Features I (Participants' gender, marital, and education characteristics) and Demographic Features II (participants' ages, the total number of years worked in their current institutions, and numbers of patients encountered daily) (SD: Standard Deviation)*

			Frequency (n)	Percentage (%)	Mean±SD
Demographic features I	Gender	Woman	203	74.6	
		Male	69	25.4	
	Marital status	Single	99	36.4	
		Married	173	63.6	
	Educational status	Primary school	2	0.7	
		Middle school	6	2.2	
		High school	31	11.4	
		University	168	61.8	
		Degree	34	12.5	
		PhD and others	31	11.4	
Demographic Features II	Age	18-24	26	9.6	
		25-34	103	37.9	
		35-44	88	32.4	35.64 ± 8.86
		45-54	52	19.1	
		55 and ↑	3	1.1	
	Total years of employment at your current institution	0.5-5	109	40.1	
		6-10	70	25.7	
		11-15	35	12.9	10.12±8.55
		16-20	21	7.7	
		21-25	18	6.6	
		26 and ↑	19	7.0	
	Number of patients you deal with daily	0	92	33.8	
		1-20	112	41.2	
		21-40	38	14.0	2.06 ±1.05
		41-60	20	7.4	
		61 and ↑	10	3.7	
	Total		272	100	

Table 2. *A comparison of work stress, work performance, and mobbing scale outcomes in terms of demographic characteristics (n=272)*

		Work Stress Scale			Work Performance			Mobbing Scale		
		Mean±SD	**t**	**p**	**Mean±SD**	**t**	**p**	**Mean±SD**	**t**	**p**
Gender	Women	3.22±1.03	2.210	0.028*	4.22±0.92	0.502	0.616	2.08±0.10	-2,612	0.010*
	Male	2.91±1.05			4.15±0.95			2.49±1.48		
Marital Status	Single	3.26±1.00	1.408	0.160	4.20±0.93	-0.022	0.982	2.32±1.23	-1.494	0.136
	Married	3.07±1.06			4.19±0.92			2.10±1.10		
Age Groups	18-24	3.36±1.07	1.855	0.119	4.36±0.96	0.951	0.435	2.12±0.88	0.697	0.595
	25-34	3.23±0.99			4.06±0.91			2.23±1.27		
	35-44	2.96±1.01			4.27±0.99			2.14±1.03		
	45-54	3.20±1.13			4.25±0.82			2.22±1.23		
	55 and ↑	2.14±0.99			4.25±0.90			1.16±0.09		
Educational Status	Primary school	2.86±0.60	0.866	0.504	4.50±0.71	1.141	0.339	1.78±0.69	0.373	0.867
	Middle School	3.47±1.29			4.10±1.01			2.54±1.30		
	High school	2.80±1.10			4.54±0.51			2.04±0.92		
	University	3.17±1.04			4.13±1.01			2.20±1.15		
	Degree	3.24±0.98			4.16±0.75			2.24±1.44		
	PhD and others	3.13±0.97			4.29±0.89			2.05±1.01		
Occupation	Physician	3.08±1.03	3.099	0.001*	4.05±0.91	0.395	0.937	2.18±1.66	0.460	0.900
	Nurse	3.50±1.02			4.17±0.97			2.16±1.01		
	Technician	2.98±1.06			4.31±0.89			2.27±1.19		
	Secretary and Data Preparation Worker	2.79±1.07			4.08±1.17			2.09±1.35		
	Patient Carer	2.63±1.05			4.38±0.83			2.11±1.07		
	Academic	3.18±0.84			4.13±1.19			2.59±0.55		
	Midwife	2.94±1.07			4.10±0.96			2.05±0.67		
	Social Worker	2.74±0.72			4.33±0.53			1.94±0.50		
	Security	3.55±1.41			4.25±0.91			2.67±1.48		
	Other	2.65±0.65			4.36±0.61			2.01±0.93		
Total years of employment at your current institution	0.5-5	3.02±0.89	0.722	0.608	4.31±0.83	2.763	0.019*	2.03±0.96	2.071	0.069
	6-10	3.26±1.14			4.10±0.92			2.41±1.27		
	11-15	3.06±1.04			3.76±1.20			2.18±1.28		
	16-20	3.31±1.11			4.31±0.93			2.66±1.55		
	21-25	3.17±1.22			4.52±0.52			2.03±1.17		
	26 and ↑	3.31±1.21			4.34±0.84			1.86±0.61		

*p < 0.05 statistically significant; **SD:** Standard Deviation

Work Stress Scale Results

Analysis showed higher exposure rates to work stress among women than men (t=2.210, p=0.028). Work Stress Scale scores varied significantly among the occupational groups (F=3.099, p=0.001). Work stress rates in the various occupations were highest in the 'others group' (administrative personnel, psychologists, pharmacists, embryologists, biologists, physiotherapists, engineers, and computer programmers), followed, in descending order, by security staff, nurses, academics, physicians, technicians, midwives, secretarial and data preparation staff, social workers, and patient carers. Since the other group comprised several occupations, the second-highest work stress level was the highest-level group. Accordingly, security staff constituted the occupation group with the highest work stress. At the same time, patient carers represented the group with the lowest work stress. No statistically significant correlations were determined between mean Work Stress Scale scores and marital status (t=-1.408, p=0.160), age (F=1.855, p=0.119), education (F=0.866, p=0.504), or total number of years worked in the most recent institution (F=0.722, p=0.608) (t=-1.408, p=0.160) (Table 2).

Work Performance Scale Results

Statistically significant differences were observed when the participants' Work Performance Scale results were

compared regarding the time they worked in their current institution (F=2.763, p=0.019). The performances of participants who had worked for 11–15 years were lower than those of the other work experience groups, the highest performance being determined in the group with 21–25 years of work experience. The work performance of the study participants increased in line with their expertise. In contrast, no significant differences in Work Performance Scale results were observed in terms of parameters such as gender (t=0.502, p=0.616), marital status (t=-0.022, p=0.982), age (F=0.951, p=0.435), education (F=1.141, p=0.339), or occupation (F=0.395, p=0.937) (Table 2).

Mobbing Scale Results

Analysis of the Mobbing Scale scores revealed that men were more exposed to mobbing than women (t=-2.612, p=0.010) (Table 2). Mobbing sub-factors were examined to the able to categorize these differences. In terms of the mobbing sub-factors (five groups), no significant gender difference was observed in the responses to the questions asked under the heading of "relationships with colleagues" (t=-1.887, p=0.060). However, significant gender differences were observed in terms of "threats and harassment" (t=-2.459, p=0.015), "work and career" (t=-2.574, p=0.011), "interference in private life" (t=-2.061, p=0.040) and "attachment to work" (t=-1.978, p=0.049). Analysis of the "threats and harassment," "work and career," "interference in private life," and "attachment to work" mobbing sub-factors revealed greater exposure to mobbing among men compared to women (p <0.05) (Table 3).

No significant differences were determined in mobbing scale scores regarding the participants' occupations (F=0.460, p=0.900). Analysis showed that 36.4% of academics, 30% of secretaries, 28.6% of security staff, 23% of technicians, 22.2% of social workers, 20.2% of nurses, 20% of midwives, 19.5% of physicians, and 15.5% of patient carers were exposed to mobbing (Table 2).

No statistically significant correlations were observed between mean Mobbing Scale scores and marital status (t=-1.494, p=0.136), age (F=0.697, p=0.592), education (F=0.373, p=0.867), or number of years worked in the most recent institution (F=2.071, p=0.069).

Number of Patients Encountered in Participants' Current Institutions and Work Stress, Work Performance, and Mobbing Scale Results

The participants 'analysis of the number of patients encountered in health institutions showed that 92 never experienced any patients, while 200 encountered at least one. The mean number of patients located daily was 2.06±1.05 (Table 1). The participants' responses indicated significant differences between stress scale scores and the number of patients encountered (F=2.622, p=0.035). Work stress was found to increase in line with the number of patients encountered (p<0.05) (Table 4). No statistically significant correlations were determined between the number of patients encountered and Work Performance Scale scores (F=2.352, p=0.054) or mobbing scale scores (F=1.943, p=0.104).

Correlations Between the Work Stress, Work Performance, and Mobbing Scales Applied

Since the study data exhibited normal distribution, correlation analysis was performed using the 'Pearson' method. Correlation analysis was applied to determine the relationship between the scales (Table 5). The study revealed a significant negative correlation between work stress and performance (p <0.05). However, no correlation was detected between mobbing and work performance or stress (p>0.05).

Table 3. *A comparison of mobbing sub-factor results by gender*

Mobbing Sub-Factors	Gender	Mean±SD	T	p
Relations with colleagues (16 Questions)	Female	2.09±1.14	-1.887	0.060
	Male	2.43±1.58		
Threats and harassment (7 Questions)	Female	1.60±1.07	-2.459	0.015*
	Male	2.02±1.65		
Work and career (8 Questions)	Female	2.31±1.38	-2.574	0.011*
	Male	2.85±1.79		
Interference in private life (4 Questions))	Female	1.94±1.40	-2.061	0.040*
	Male	2.36±1.70		
Commitment to work (2 Questions)	Female	2.97±1.91	-1.978	0.049*
	Male	3.49±1.75		

*p <0.05 statistically significant; SD: Standard Deviation

Table 4. *A statistical comparison of work stress, work performance, and mobbing scale results in terms of the number of patients encountered daily*

Scale	Number of patients encountered daily	Mean±SD	F	p
Work stress	0	2.86±0.88		
	1-20	3.28±1.03		
	21-40	3.31±1.19	2.622	0.035*
	41-60	3.28±1.11		
	61 and ↑	3.11±1.37		
Work performance	0	4.36±0.71		
	1-20	4.02±1.09		
	21-40	4.17±0.88	2.352	0.054
	41-60	4.25±0.79		
	61 and ↑	4.65±0.61		
Mobbing	0	2.29±1.96		
	1-20	2.01±0.96		
	21-40	2.55±1.57	1.943	0.104
	41-60	2.03±1.16		
	61 and ↑	1.97±1.46		

*p < 0.05 statistically significant; SD: Standard Deviation

Regression Analysis Results between the Work Stress, Work Performance, and Mobbing Scales

Multivariate regression analysis was applied to evaluate the responses to the questionnaire of the participants working in any health institution. Univariate analysis would have been used in the presence of only one variable. However, multivariate analysis was employed since this study included more than one variable. A regression analysis was performed between mobbing, work stress, and work performance (Table 5). The responses provided by the individuals working in health institutions revealed a 1% (0.001) significance level between mobbing and work stress and work performance. No statistically significant association was found between mobbing and work stress and work performance (p>0.05).

Multivariate regression analysis was also applied to the relationship between work performance, mobbing, and work stress (Table 5). The responses provided by the individuals working in health institutions revealed a 1.9% (0.001) significance level between mobbing and work stress and work performance. The analysis showed no significant relationship between work performance and mobbing (p=0.789), while a significant negative association was observed between work performance and work stress (p=0.025). A powerful direct negative correlation thus emerged between work performance and work stress.

Multivariate analysis was also applied to the relationship between work stress, mobbing, and work performance (Table 5). The responses provided by the individuals working in health institutions revealed a 1.9% (0.001) significance level between mobbing and work stress and work performance. The analyses revealed no significant association between work stress and mobbing (p=0.729), while a significant negative association between work stress and work performance (p=0.025). A powerful direct negative correlation thus emerged between work stress and work performance.

Discussion

This study evaluated mobbing, work stress, and work performance among individuals working in any health institution in Türkiye. A comparison of the responses from the entire participant group (n=272) revealed a general mean mobbing scale score of 2.18. This available mean value lay within the margins of 'I Disagree" on the seven-point Likert-type scale. In light of these findings, the participants in the study were not, as a group, exposed to significant mobbing. However, a

Table 5. *Correlation and multiple regression analysis between work stress, work performance, and mobbing*

CORRELATION ANALYSIS				
		Work stress	**Work performance**	**Mobbing**
	Work stress	1	-0.136*	-0.019
	Work performance	-0.136*	1	-0.014
	Mobbing	-0.019	-0.014	1
MULTIPLE REGRESSION ANALYSIS				
Independent variables		ß	t	p
DV: Mobbing	**Work stress**	-0.021	-0.347	0.729
IV: Work stress and work performance	**Work performance**	-0.016	-0.268	0.789
DV: Performance **IV:** Mobbing and work stress	**Work stress**	-0.137	-2.260	0.025*
	Mobbing	-0.0136	-0.268	0.789
DV: Work stress **IV:** Mobbing and work stress	**Work performance**	-0.154	-2.260	0.025*
	Mobbing	-0.019	-0.347	0.729

DV: Dependent variable; IV: Independent variables; **ß:** Beta; *p < 0.05 statistically significant, n=272.

detailed examination of the responses showed that health workers were exposed to mobbing. The answers given by the participants regarding occupational groups were therefore evaluated based on scores of 2.72–3.57 (Somewhat Agree) or above on the seven-point Likert-type scale. This analysis showed that 36.4% of academics, 30% of secretaries, 28.6% of security staff, 23% of technicians, 22.2% of social workers, 20.2% of nurses, 20% midwives, 19.5% of physicians, and 15.4% of midwives were exposed to mobbing.

Studies have reported that members of several occupation groups working in health institutions experience mobbing[17,18]. Mobbing was detected in nine of the 18 occupational groups involved in the present study. Surprisingly, academics were the occupational group with the highest rate of exposure to mobbing, at 36.4%. One previous study evaluated 400 academics in 10 public universities and found that 66.8% of the participants were subjected to mobbing[19]. Another study observed statistically significant academic mobbing among the 135 participants assessed[20]. As a result of the present research, this state of affairs remained the same in terms of academics working in health institutions.

A comparison of demographic characteristics showed that men were exposed to greater mobbing than women. In contrast, previous studies have reported that women are more exposed to mobbing among individuals working in health institutions than men[21]. Another study involving academics working in health institutions reported no gender difference in mobbing[22]. In the present study, statistical analysis revealed that men were exposed to greater mobbing than women. We think this may be due to a higher employment rate in health institutions among men. In particular, while nursing was exclusive to women at one time, the number of male nurses has increased in recent years. Studies have shown that male nurses are more exposed to physical[23,24], emotional, and sexual harassment and aggression[25] than women. We also think that questionnaires being completed online allowed male participants to respond more freely.

No significant gender difference was determined regarding the mean responses to the questions asked under the 'relationships with colleagues' subheading. However, gender was statistically significantly associated with 'threats and harassment' , 'work and career' , 'interference in private life' , and 'attachment to work' . The mobbing sub-factors of 'threats and harassment,' 'work and career,' 'interference in private life,' and 'attachment to work' were all greater in men than in women.

No significant association was determined between mobbing and participants' age groups, marital status, education, number of patients encountered daily, or years worked. In contrast, previous studies have reported significant associations between mobbing and age, education, marital status, years worked, and patient numbers[26]. No significant associations were found in the present study, which we think may be related to the demographic characteristics of the study groups.

Work stress was also evaluated in addition to mobbing. A five-point Likert-type scale was employed to calculate the response scores when performing that evaluation. The general mean score for the questions in the Work Stress Scale was 3.14. According to the five-point Likert scale, that value was within the limits of 'Undecided'. This may indicate a high probability of work stress among the 272 individuals in the study. Had the mean scale score been 2.60 or lower, we would have concluded that the participants had no work stress.

Analysis revealed significant differences in Work Stress Scale scores regarding the different occupational groups. According to the results of our study, security staff was determined to be the occupation group with the highest work stress levels. Previous studies have reported higher work stress among nurses[27], physicians[17], technicians, and auxiliary nurses[28]. Another study found more significant work stress among physicians, administrative personnel, nurses, health technicians/technicians, and technical services staff, women, and workers in administrative units[29]. Studies have thus shown the presence of work stress in several occupation groups working in health institutions. Our literature scan revealed that one study involving 130 individuals working as private security staff across the province of Izmir determined a work stress rate of 55%[30]. However, a comparison between different professions was not made in this study. In comparative studies among individuals working in health institutions, no study found that the stress level of the security guard was too high.

Gender analyses in the present study revealed more significant work stress among women than men. This is consistent with previous research. Özcan et al.[29] investigated various occupations, including physicians, administrative personnel, nurses, health technicians/technicians, and technical services staff. Also, they found that women experienced more significant work stress. Participants' work-stress scale scores differed significantly regarding the number of patients

encountered. Work stress increased in line with patient numbers. Vahedian-Azimi et al.[31] found that stress was not affected due to raised patient beds in the pediatric department. This indicates that there is no association between patient numbers and work stress. In another study, however, every additional patient following a determination of the standard number of patients per nurse increased the probability of burnout among working individuals by 23%[32]. Despite the inconsistencies among different studies, generally, a low number of health workers in proportion to patient numbers or an unexpected rise in patient numbers exacerbates work stress. Indeed, studies have shown that work stress increased due to patient numbers in health institutions following the COVID-19 pandemic[33,34].

No statistically significant variations in work stress were observed regarding marital status, age groups, education, or number of years worked. However, some previous studies have reported that health workers aged 30–39 experience the highest level of work stress[35]. In the present study, however, no significant associations were determined between the sociodemographic characteristics of age, marital status, education, and stress. We think this may be due to differences in the demographic characteristics of the groups examined. Vahedian-Azimi[31] observed no effect of education levels on work stress. This finding is consistent with the present study.

Since the present study investigated factors impacting performance, such as work stress and mobbing, performance evaluation was also conducted. The general mean score for the questions in the work performance scale was 4.20. This general mean corresponds to 'I Strongly Agree' on the five-point Likert-type scale. This means that work performance among the 272 participants was very high. A study examining the performance of nurses in telemedicine (remote diagnosis and patient treatment using telecommunication technology) also reported high performance[36]. In contrast, Tong[37] reported low motivation among hospital nurses and that this, in turn, affected their performance. Another study stated that mobbing is one of the most important reasons for poor performance[38].

No statistically significant variations in work performance scale scores were determined in terms of demographic factors such as occupation, sex, marital status, age, education, or daily numbers of patients encountered. One study evaluating performance in a health institution reported that while sociodemographic characteristics exhibited no effect, physical conditions did impact performance[39]. Doubtless, the same results are not obtained from every health institution.

A significant association was determined between participants' work performance scale scores and the total years worked in the most recent institution. Workers with 11–15 years' experience exhibited lower performance than those with 21–25 years' experience. We think that performance increases in line with the number of years worked. One previous study examined a group of 3098 nurses and reported lower performance among those with a mean experience greater than 25.7 years. The authors concluded that long-term work resulted in burnout and impacted performance[40]. Performance was improved in one study that employed reducing stress by providing education for nurses who had recently started working. The education sessions were reported to lower education and thus increase performance, with a negative correlation between the two[41]. This may also be an indicator for the present study. Performance may have increased due to increased experience as the number of years worked increased and decreased work stress.

Correlation analysis revealed a significant negative relationship between work stress and work performance, while no correlation was found between mobbing and work performance or work stress. The responses provided by the individuals working in health institutions revealed a 1.9% significance level between mobbing and work stress and work performance. Regression analysis showed no association between work performance and mobbing, while a negative effect regression relationship was observed between work performance and work stress. Duman and Akdemir[42] reported a significant negative correlation between mobbing and worker performance. Another study reported that mobbing levels adversely impacted performance and stress[43]. However, the present study observed no significant association between work stress or performance and mobbing. Another study on the subject was consistent with our findings. Studies of the relationships between work stress and performance have reported a negative association between them[41]. This is compatible with our results.

The mean responses given by the participants to the questions contained in these scales showed no association between mobbing and work stress or work performance. However, an adverse effect relationship was found between work stress and work performance.

Strengths and Limitations

This research presents several overarching strengths. The number of studies examining work performance, work stress, and mobbing together is limited in the literature. Moreover, our study may reflect the general nature of healthcare workers' work performance, work stress, and mobbing in Türkiye because it is a multicenter study involving seven regions (Marmara, the Aegean, the Black Sea, Central Anatolia, the Mediterranean, and Southeast Anatolia).

However, the study also had several limitations. It was aimed to include all healthcare professionals nationwide, but there was limited participation. Besides, only the short-term effects of work performance work stress on health workers could be determined. The long-term effects of work performance and stress on healthcare workers are unknown. Therefore, the long-term experiences of the research subjects would be a valuable avenue to explore in the future.

Acknowledgments

We thank all the health workers who participated in this study.

Authors' Contribution

The authors share the responsibility for the manuscript.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare no potential conflicts of interest regarding this article.

Disclaimer

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Funding Information

The authors received no financial support for the research.

References

1. Leymann H. The content and development of mobbing at work. European Journal of Work and Organizational Psychology. 1996;5:165–184.
2. Leymann H, Annelie G. Mobbing at work and the development of post-traumatic stress disorders. European Journal of Work and Organizational Psychology. 2008;5:251–275.
3. Tunçer P. Örgütlerde performans değerlendirme ve motivasyon. Sayıştay Dergisi. 2013;88:87–108.
4. Siegrist j, Rode A. Work stress and health risk behavior. Scand J Work Environ Health. 2006;32(6, special issue) :473–481.
5. Lynch JW, Kaplan GA, Cohen RD, Tuomilehto J, Salonen JT. Do cardiovascular risk factors explain the relation between socioeconomic status, risk of all-cause mortality, cardiovascular mortality, and acute myocardial infarction? Am J Epidemiol. 1996;144:934–42.
6. Özen Y, Gül A. Population-sampling issue on social and educational research studies. Atatürk Üniversitesi Kazım Karabekir Eğitim Fakültesi Dergisi. 2007;15:394–422.
7. Noy C. Sampling knowledge: the hermeneutics of snowball sampling in qualitative research. International Journal of Social Research Methodology. 2008;11:327–344.
8. Punch KF. Introduction to social research: quantitative and qualitative approaches. SAGE basım yayım dağıtım, (3th ed., pp. 1–327). 1998;London.
9. House RH, Rizzo JR. Role conflict and ambiguity as critical variables in a model of organizational behavior organ. Behav. Hum. Perform. 1972;7:467–505.
10. Efeoğlu İE, Özgen H. İş-aile yaşam çatışmasının iş stresi, iş doyumu ve örgütsel bağlılık üzerindeki etkileri: ilaç sektöründe bir araştırma. Çukurova Üniversitesi Sosyal Bilimler Enstitüsü Dergisi. 2006;16:237–254.
11. Kirkman BL, Rosen B. Beyond self-management: antecedents and consequences of team empowerment. Academy of Management Journal. 1999;42:58–74.
12. Sigler TH, Pearson CM. Creating an empowering culture: examining the relationship between organizational culture and perceptions of empowerment. Journal of Quality Management. 2000;5:27–52.
13. Çöl G. Algılanan güçlendirmenin işgören performansı üzerine etkileri. Doğuş Üniversitesi Dergisi. 2008;9:35–46.
14. Aiello A, Dientinger P, Nardella C, Bonafede M. A tool for assessing the risk of mobbing in organizational environments: the "Val. Mob. " scale. Prevention Today. 2008;3:9–24.
15. Laleoğlu A, Özmete E. Mobbing ölçeği: geçerlik ve güvenirlik çalışması. Sosyal Politika Çalışmaları. 2013;13:9–31.
16. Kilic S. Cronbach'ın alfa güvenirlik katsayısı. Journal of Mood Disorders. 2016;6:47–48.
17. Sun T, Gao L, Li F, Shi Y, Xie F, Wang J, et al. Workplace violence, psychological stress, sleep quality and subjective health in Chinese doctors: a large cross-sectional study. BMJ Open. 2017;7:7:e017182, 1–8.

18. Campo VR, Klijn TP. Verbal abuse and mobbing in pre-hospital care services in Chile. Rev Lat Am Enfermagem. 2018;8:25:e2956.
19. Çögenli MZ, Asunakutlu T. Akademide mobbing: adım üniversiteleri örneği. Erzincan Üniversitesi Sosyal Bilimler Enstitüsü Dergisi (ERZSOSDE). 2016;IX-I:17–32.
20. Softa KH, Bukeç E, Çolak A, Göçer D. Akademisyenlerin mobbing durumlarının incelenmesi. Ege Üniversitesi Hemşirelik Fakültesi Dergisi. 2016;32:34–47.
21. Weber A, Hörmann G, Köllner V. Mobbing-a work related risk factor of service-based society? Gesundheitswesen. 2007;69:267–276.
22. Yıldırım D, Yıldırım A. Sağlık alanında çalışan akademisyenlerin karşılaştıkları psikolojik şiddet davranışları ve bu davranışların etkileri. Türkiye Klinikleri Tıp Bilimleri Dergisi. 2010;30:559–570.
23. Tracey C, Honor N. The multifaceted ınfluence of gender in career progress in nursing. Journal of Nursing Management. 2007;15:677–682.
24. Loughrey M. Just how male are male nurses? Journal of Clinical Nursing. 2008;17:1327–1334.
25. Andrews ME, Stewart NJ, Morgan D G, et al. More alike than different: a comparison of male and female rns in rural and remote Canada. Journal of Nursing Management. 2012;20:561–570.
26. Karsavuran S. Sağlık sektöründe mobbing: hastane yöneticileri üzerinde bir uygulama. Mustafa Kemal Üniversitesi Sosyal Bilimler Enstitüsü Dergisi. 2014;26:271–296.
27. Khamisa N, Oldenburg B, Peltzer K, Ilic D. Work related stress, burnout, job satisfaction and general health of nurses. Int J Environ Res Public Health. 2015;12:652–666.
28. Ribeiro RP, Marziale MHP, Martins JT, Galdino M. JQ, Ribeiro PHV. Occupational stress among health workers of a university hospital. Rev Gaucha Enferm. 2018;23:39:e65127.
29. Özcan EM, Ünal A, Çakıcı AB. Sağlık çalışanlarında işe bağlı stres: Konya Numune Hastanesi saha çalışması. Aksaray Üniversitesi İktisadi ve İdari Bilimler Fakültesi Dergisi. 2014;7:125–131.
30. Ersezgin RE, Tok ES. Algılanan iş stresi, psikolojik dayanıklılık, başa çıkma stilleri ve öz-duyarlılığın tükenmişlik düzeyini yordayıcı etkisi. Uludağ Üniversitesi Fen-Edebiyat Fakültesi Sosyal Bilimler Dergisi. 2019;36:1–36.
31. Vahedian-Azimi A, Hajiesmaeili M, Kangasniemi M, Fornés-Vives J, Hunsucker RL, Rahimibashar F, et al. Effects of stress on critical care nurses: a national cross-sectional study. J Intensive Care Med. 2019;34(4):311–322.
32. Aiken LH, Clarke SP, Sloane DM, Sochalski J, Silber JH. Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. JAMA. 2002;288:1987–1993.
33. Mo Y, Deng L, Zhang L, Lang Q, Liao C, Wang, et al. Work stress among Chinese nurses to support Wuhan in fighting against COVID-19 epidemic. Nurs Manag. 2020;28:1002–1009.
34. Keleş Aİ, Keleş G. A Comparative analysis of world health systems and Covid-19. Journal of Experimental and Clinical Medicine. 2021;38(2):115–120.
35. Atasoy A, Yorgun S. Sağlık çalışanlarında iş gerilimi ve iş stres düzeyinin değerlendirilmesi. Sağlıkta Performans ve Kalite Dergisi. 2013;6:71–88.
36. Souza CFQ, Oliveira DG, Santana ADDS, Mulatinho LM, Cardoso MD, Pereira EB, et al. Evaluation of nurse's performance in telemedicine. Rev Bras Enferm. 2019;19:933–939.
37. Tong L. Relationship between meaningful work and job performance in nurses. Int J Nurs Pract. 2018;24:e12620.
38. Duman Ç. M., Akdemir B. Mobbing ve çalışan performansı arasındaki ilişkiyi belirlemeye yönelik bir araştırma. Journal of Academıc Approaches. 2016;7:29–52.
39. Uzuntarla Y, Ceyhan S, Fırat İ. Çalışan performansının incelenmesi: Sağlık sektörü örneği. Gülhane Tıp Dergisi. 2017;59:16–20.
40. Dyrbye LN, Shanafelt TD, Johnson PO, Johnson LA, Satele D, West CP. A cross-sectional study exploring the relationship between burnout, absenteeism, and job performance among American nurses. BMC,. 2019;21:18–57.
41. Al-Ghareeb A, McKenna L, Cooper S. The influence of anxiety on student nurse performance in a simulated clinical setting: A mixed methods design. Int J Nurs Stud. 2019;98:57–66.
42. Duman MÇ, Akdemir B. Mobbing ve çalışan performansı arasındaki ilişkiyi belirlemeye yönelik bir araştırma. Journal of Academıc Approaches. 2016;7:29–52.
43. Kesebir M. Mobbing'in çalışanların performansı üzerine etkisi: İstanbul'da bankacılık sektörü üzerine bir uygulama. Uşak Üniversitesi Sosyal Bilimler Dergisi. 2018;6:54–169.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Assessment of Picky Eating, Emotional Eating and Body Perception in Healthy Individuals

Sağlıklı Bireylerde Seçici Yeme, Duygusal Yeme ve Beden Algısının Değerlendirilmesi

Izzet Ulker[1], Kubra Esin[2], Suleyman Kose[3], Bartu Eren Gunesliol[4], Feride Ayyildiz[5]

[1]Department of Nutrition and Dietetics, Faculty of Health Sciences, Erzurum Technical University, Erzurum; [2]Department of Nutrition and Dietetics, Faculty of Health Sciences, Tokat Gaziosmanpasa University, Tokat; [3]Department of Nutrition and Dietetics, Faculty of Health Sciences, Artvin Coruh University, Artvin; [4]Department of Nutrition and Dietetics, Faculty of Health Sciences, Duzce University, Duzce; [5]Department of Nutrition and Dietetics, Faculty of Health Sciences, Gazi University, Ankara, Türkiye

ABSTRACT

Aim: *This study investigated the association between choosy eating, emotional eating, and body image in healthy individuals.*

Materials and methods: *This study was conducted with 639 people [385(60.3%) women and 254 (39.7%) men] aged 18–60 years through online surveys. The Stunkard Figure Rating Scale assessed how people see their bodies. Adult Picky Eating Questionnaire (APEQ) was used to determine picky eating behaviors and attitudes. The Emotional Eater Scale was also used to assess eating behaviors. Anthropometric measurements of body weight and height were taken on a self-reported basis. One-way ANOVA was used to analyze the differences between the groups.*

Results: *While 23.8% of the participants were satisfied with their body image, 76.2% were unsatisfied with their body image (61.5% wanted to lose body weight, 14.7% wanted to gain body weight). Body image dissatisfaction was found to be associated with emotional eating and its sub-dimensions ($p<0.05$). According to the body mass index (BMI) classification, a statistically significant difference was discovered between the total score of picky eating and the total score of emotional eating between underweight and obese people ($p<0.05$).*

Conclusion: *Picky eating is associated with emotional eating, body weight, and body perception. It is thought that there is a need to evaluate depression, anxiety, stress, and quality of life parameters in future face-to-face studies.*

Keywords: picky *eating; emotional eating; body image*

ÖZET

Amaç: *Bu çalışmanın amacı, sağlıklı bireylerde beden imajı, duygusal yeme ve seçici yeme arasındaki ilişkinin incelenmesidir.*

Materyal ve Metot: *Bu çalışma, 18–60 yaş aralığındaki 639 kişiyle [385(%60,3) kadın ve 254 (%39,7) erkek] çevrimiçi anket yoluyla gerçekleştirilmiştir. Beden imajı algısı Stunkard Beden İmajı Derecelendirme Ölçeği ile değerlendirildi. Seçici yeme davranış ve tutumlarını değerlendirmek için Yetişkin Seçici Yeme Anketi (APEQ) kullanıldı. Yeme davranışlarını değerlendirmek için Duygusal Yeme Ölçeği de kullanıldı. Vücut ağırlığı ve boy uzunluğuna ilişkin antropometrik ölçümler kişisel bildirim esasına göre alınmıştır. Gruplar arasındaki farkı analiz etmek için tek yönlü ANOVA testi kullanılmıştır.*

Bulgular: *Katılımcıların %23,8'i beden imajından memnun iken, %76,2'si beden imajından memnun değildi (%61,5'i kilo vermek, %14,7'si kilo almak istiyordu). Beden imajından memnuniyetsizliğin duygusal yeme ve alt boyutlarıyla ilişkili olduğu belirlenmiştir ($p<0,05$). Beden kitle endeksi (BMI) sınıflamasına göre zayıf ve obez olanlar arasında seçici yeme toplam puanı ile duygusal yeme toplam puanı arasında istatistiksel olarak anlamlı fark bulunmuştur ($p<0,05$).*

Sonuç: *Seçici duygusal yeme, vücut ağırlığı ve beden algısı ile ilişkilidir. Gelecekte yapılacak yüz yüze çalışmalarda depresyon, anksiyete, stres ve yaşam kalitesi parametrelerinin değerlendirilmesine ihtiyaç olduğu düşünülmektedir.*

Anahtar kelimeler: *seçici yeme; duygusal yeme; beden imajı algısı*

İletişim/Contact: *Izzet Ulker, Department of Nutrition and Dietetics, Faculty of Health Sciences, Erzurum Technical University, Yakutiye, Erzurum, Türkiye* • ***Tel:*** *0544 219 87 38* • ***E-mail:*** *izzet.ulker@erzurum.edu.tr* • ***Geliş/Received:*** *21.09.2023* • ***Kabul/Accepted:*** *04.01.2024*

ORCID: *İzzet Ülker: 0000-0001-9444-5243 • Kübra Esin: 0000-0002-2687-1811 • Süleyman Köse: 0000-0003-1914-2140 • Bartu Eren Güneşliol: 0000-0002-0472-7835 • Feride Ayyıldız: 0000-0003-2828-3850*

Introduction

Healthy eating is one of the most essential health-related behavioral factors targeted by many interventions in public health and health promotion. Unhealthy eating habits can increase the risk of many chronic diseases, particularly cardiovascular disease, diabetes, and cancer[1]. Eating behaviors such as emotional eating (EA) and picky eating (PY) are among the conditions that are effective in the emergence of inappropriate eating habits[2]. Picky eating is an eating attitude characterized by consuming a specific variety of foods to avoid or completely oppose the consumption of known and previously untasted foods[3]. Estimates for the prevalence of picky eating in children and adults range from 15 to 45%[4]. A severe picky diet is associated with poor nutritional intake, such as insufficient vitamins E and C.

Additionally, different levels of picky eating severity must be measured[5]. Despite not being classified as an eating disorder, EA is linked to anxiety and eating-related psychosocial impairment[6]. This situation negatively affects the quality of life and health of individuals[7]. Picky eating is reported to be one of the restrictive eating patterns that can lead to symptoms of Avoidant/Restrictive Food Intake Disorder (ARFID) in DSM-V. All ages can be affected by ARFID, which can result in insufficient caloric intake and/or dietary variety, body weight loss, nutrient deficiencies, dependency on nutritional supplements, and/or psychological damage[8]. The term "emotional eating" refers to the propensity to eat excessive amounts of food even when not hungry as an instinctual reaction to unpleasant feelings[9,10]. This type of food consumption habit is also reported to be associated with anxiety and depression for all age groups[11]. Emotional situations affect the quantity and quality of food consumption. Negative Emotional situations such as stress and depression are more often associated with increased food intake but less commonly with a complete loss of appetite[12,13]. Generally, it is emphasized that individuals tend to consume more high-fat and high-carbohydrate foods to cope with negative emotional states such as anxiety[14]. Such habitual eating habits lead to the emergence of obesity, which is the precursor of many chronic diseases[15]. Obesity can also result in body image dissatisfaction[16]. Obese people experience unfavorable clinical effects from body image dissatisfaction, which have an impact on their behavior, quality of life, and mental health. In various psychological dimensions, mainly concerning body image dissatisfaction, overweight and obese people report lower than average quality of life and poor perceived health status[17,18].

Eating behavior disorders may be a risk factor for obesity and may also lead to malnutrition. In this context, SY, which is one of the eating behavior disorders classified as part of the spectrum of nutritional difficulties and affects food preferences, is a multidimensional phenomenon that is behaviorally and etiologically different from other types of eating disorders[19]. Studies evaluating the relationship between picky eating, emotional eating and body image disturbance are limited in the literature. This study assesses the connection between picky eating, emotional eating, and disturbed body image in healthy individuals.

Materials and Methods

This study was conducted on 639 individuals, 385 (60.3%) women and 254 (39.7%) men, aged between 18–60 years. The study was conducted online between November 2022 and February 2023 among adults aged 18. The sample size was determined by snowball sampling, where the future sample was recruited by linking the current sample. Data were collected via online Google Forms, socio-demographic characteristics (demographic characteristics such as age, education level, gender, and health information about their health status and general eating habits), Stunkard Figure Rating Scale, Adult Picky Eating Scale, and Emotional Eater Questionnaire. At the beginning of the form, the acceptance of participation in the study was questioned, and the form was opened to the individuals who accepted.

Stunkard Figure Rating Scale

The Stunkard Scale for body image perception was developed by Stunkard et al.[20] in 1983. The scale comprises male and female silhouettes ranging from very thin to extremely obese. The respondents were asked if the numbered silhouette was most similar to their body size and if they would like to look like the silhouette in the number. The body satisfaction of the participants was found by evaluating the difference between the number they indicated and the number they wanted to be. The difference between the two states expresses the body satisfaction of the individuals. If the difference is positive, individuals want to gain body weight; if the difference is negative, they want to lose body weight; if the difference is zero, they are satisfied with their bodies[20]. If the score difference between the pictures is positive, it indicates that they would like to gain body weight, if the difference is negative, they would like to

gain body weight; and if the difference is zero, they are satisfied with their bodies.

Adult Picky Eating Questionnaire

The Adult Picky Eating Questionnaire (APEQ) was developed by Ellis et al. in 2017 to assess picky eating attitudes and behaviors in adults[6]. Turkish validity and reliability were conducted by Ayyildiz et al.[21].

Although the APEQ, developed for adult individuals, initially consists of 16 questions[6], the Turkish version consists of 14. Meal Presentation, Food Variety, Meal Disengagement, and Taste Aversion are the four subdimensions. Each question is graded using a 5-point Likert-type scale, with 1 being "Never" and 5 being "Always." Picky eating behavior and attitude were linked to higher total scores on the questionnaire.

Emotional Eater Questionnaire

The questionnaire was developed by Garaulet et al. to assess emotional eating behaviors[22]. The Emotional Eater Questionnaire consists of 10 items and three subdimensions. Disinhibition, type of food, and guilt are the three subscales that comprise the questionnaire's 10 items. A 4-point Likert-type scale is used to evaluate the questionnaire. ("0" Never, "1" On occasion, "2" Typically, and "3" Continually). "0" represents the lowest score, and "30" represents the highest. High scores on the scale indicate a high level of emotional eating habits. The scale's internal consistency coefficient, or Cronbach's alpha, was calculated to be 0.84[22].

The validity study of the scale was conducted by Arslantaş et al. in Türkiye. The Turkish translation of the Emotional Eater Questionnaire is considered a valid and reliable measurement tool. With these features, it is appropriate to use the EES in research. In addition, it is also relevant to apply the validity and reliability study of the scale in special conditions such as obesity, depression, stress, and anxiety[23].

Assessment of Anthropometric Measurements

The participant's body weight (kg) and height (cm) values were recorded based on the individuals' declarations. The participant's body weight and height were used to calculate their BMI. The formula "BMI=Body weight (kg)/Height (m^2)" was used to make the determination. Underweight people were those who weighed less than 18.50 kg/m^2, normal people were those who weighed between 18.50 and 24.99 kg/m^2, overweight people were those who weighed between 25.0 and 29.99 kg/m^2, and obese people were those who weighed more than 30 kg/m^2 [24].

Statistical Analysis

For the study's statistical analysis, IBM Statistical Package for Social Sciences (SPSS) program version 25 was employed. Kolmogorov-Smirnov / Shapiro-Wilk tests, normal q-q plot graphs, and histogram graphs were used to assess whether the variables were compatible with a normal distribution. Quantitative factors were summarized as mean and standard deviation, whereas qualitative variables were summarized as number (n) and percentage (%). One-way ANOVA analysis was utilized since the dependent variables used in the study had features of a normal distribution. The 5% level of statistical significance was chosen.

Results

With a total of 639 participants, the study was completed. Table 1 lists the general characteristics of the participants. The average age of the participants was 30.81±10.9 years; 60.3% were female, and 39.7% were male. According to BMI classification, 4.9% were underweight, 55.1% were normal, 27.7% were pre-obese, and 12.4% were obese. The total emotional eating scores of the participants were 10.8±5.61, picky eating total score was 36.6±7.1 and meal presentation, food variety, meal disengagement, and taste aversion scores were 19.2±4.17, 7.3±2.43, 5.4±1.53 and 4.6±1.73, respectively.

Table 2 analyzes the total and subscale scores of the picky eating questionnaire scores for adults and the emotional eater questionnaire scores of the research participants according to BMI classification. The overall score of the emotional eater questionnaire, the difference in the total score and subscale scores of the adult picky eating scale, and the taste aversion all showed statistically significant differences based on BMI categorization. Pre-obese and obese people have higher APEQ total scores than healthy people ($p<0.05$).

While 23.8% of the participants were satisfied with their body image, 76.2% were unsatisfied with their body image (61.5% wanted to lose body weight, while 14.7% wanted to gain body weight). The total and subscale scores of the adult picky eating questionnaire and emotional eater questionnaire scores in adults according to the body image perception of the individuals

Table 1. *General Characteristics of Participants (n: 639)*

	n	%
Sex		
Women	385	60.3
Men	254	39.7
Marital status		
Married	223	34.9
Single	416	65.1
Education status		
Primary school	17	2.6
Middle school	32	5
High school	63	9.9
University	448	70.1
Postgraduate	79	12.4
Smoking		
Yes	153	23.9
No	486	76.1
Alcohol		
Yes	94	14.7
No	545	85.3
Body Mass Index (BMI) Classification		
Weak (<18.5)	31	4.9
Normal (18.5–24.9)	352	55.1
Pre-obese (25.0–29.9)	177	27.7
Obese (≥30.0)	79	12.4
Body Image Perception		
Those who want body weight gain	94	14.7
Those who are satisfied with their body image	152	23.8
Those who want body weight loss	393	61.5
	$\bar{X} \pm SS$	**Min-Max**
BMI (kg/m^2)	24.4±4.33	15.4–41.4
Age (years)	30.8±10.98	20.0–60.0
Emotional eater questionnaire (Total)	10.8±5.61	0.0–30.0
Disinhibition	6.2±3.65	0–6.0
Type of food	2.7±1.36	0–6.0
Guilt	1.9±1.44	0–18.0
Adult picky eating questionnaire (Total)	36.6±7.1	14.0–68.0
Meal presentation	19.2±4.17	7.0–33.0
Food variety	7.3±2.43	3.0–15.0
Meal disengagement	5.4±1.53	2.0–8.0
Taste aversion	4.6±1.73	2.0–10.0

n: Number of participants

Table 2. *Evaluation of total and subscale scores of the Adult Picky Eating Questionnaire and Emotional Eater Questionnaire scores according to BMI classification of participants*

Questionnaires	**Body mass index (BMI) classification**	$\bar{X} \pm SS$	**Statistical analysis**	
			F	**p**
Adult picky eating questionnaire (Total)	Weak[a,b]	35.2±8.47	4.461	0.004
	Normal[a]	35.9±6.85		
	Pre-obese[b]	37.7±6.73		
	Obese[b]	38.3±8.17		
Meal presentation	Weak	18.6±4.31	2.539	0.060
	Normal	18.9±3.82		
	Pre-obese	19.7±4.23		
	Obese	20.2±5.17		
Food variety	Weak	6.9±3.42	2.338	0.077
	Normal	7.1±2.42		
	Pre-obese	7.6±2.22		
	Obese	7.7±2.36		
Meal disengagement	Weak	5.6±1.86	0.386	0.763
	Normal	5.4±1.56		
	Pre-obese	5.4±1.46		
	Obese	5.5±1.40		
Taste aversion	Weak[a]	3.9±1.50	5.822	**0.001**
	Normal[a,c]	4.4±1.78		
	Pre-obese[b]	4.9±1.69		
	Obese[b,c]	4.9±1.51		
Emotional eater questionnaire (Total)	Weak[a]	8.5±4.53	2.859	**0.036**
	Normal[a,b]	11.6±6.45		
	Pre-obese[b]	11.3±5.62		
	Obese[b]	11.5±6.49		
Disinhibition	Weak[a]	4.7±2.95	6.464	**0.003**
	Normal[a,b]	5.9±3.55		
	Pre-obese[b]	6.6±6.64		
	Obese[b]	7.1±4.12		
Type of food	Weak	2.5±1.20	0.888	0.447
	Normal	2.8±1.37		
	Pre-obese	2.7±1.36		
	Obese	2.7±1.36		
Guilt	Weak	1.4±1.29	2.068	0.103
	Normal	1.8±1.43		
	Pre-obese	2.0±1.38		
	Obese	1.9±1.66		

As a result of the homogeneity evaluation, The Tukey HSD test was used to determine the difference between homogeneous groups, and the Tamhane T2 test was used in non-homogeneous groups.
* Different letters indicate the statistical difference.

participating in the study are given in Table 3. The total score of the emotional eater questionnaire was higher in those who wanted body weight loss than in those who wanted weight gain ($p<0.05$).

Discussion

Picky eating behavior has recently increased in prevalence, and nutrient deficiencies[5], body weight, mood disorders[5,25], and diminishing quality of life[7] are associated with these disorders. Adult picky eaters are more likely to score in the clinical range for depression and OCD than their non-picky colleagues do, according to recent studies[7,26,27]. However, the mechanism of this relationship is not clear[25]. These mood disturbances may affect individuals' emotional eating and body image. This study examined the association between picky eating, emotional eating, and problems with body image in healthy persons.

Table 3. *Evaluation of total and subscale scores of the Adult Picky Eating Questionnaire and Emotional Eater Questionnaire scores according to body image perception of participants*

Questionnaires	Classification according to body image perception		Statistical Analysis	
		$\overline{X}$ ± SS	F	p
Total Scores for Picky Eating	1	37.7±6.86	0.607	0.545
	0	36.4±8.12		
	-1	36.5±6.8		
Meal Presentation	1	19.2±3.95	0.093	0.911
	0	19.4±4.42		
	-1	19.2±4.12		
Food Variety	1	7.7±2.45	1.186	0.306
	0	7.1±2.62		
	-1	7.3±2.3		
Meal Disengagement	1[a]	5.9±1.65	7.660	**0.001**
	0[b]	5.9±1.59		
	-1[b]	5.4±1.59		
Taste Aversion	1	4.5±1.72	0.150	0.860
	0	4.5±1.92		
	-1	4.6±1.66		
Emotional Eater Questionnaire (Total)	1[a]	8.3±4.89	33.844	**<0.01**
	0[b]	12.2±4.61		
	-1[b]	12.1±5.7		
Disinhibition	1[a]	4.6±3.21	32.091	**<0.01**
	0[b]	4.9±3.10		
	-1[b]	7.1±3.69		
Type of food	1[a]	2.4±1.26	10.077	**<0.01**
	0[b]	2.4±1.25		
	-1[b]	2.9±1.39		
Guilt	1[a]	1.3±1.25	25.966	**<0.01**
	0[b]	1.4±1.14		
	-1[b]	2.2±1.45		

The Welch F test was calculated for groups without homogeneity. As a result of the homogeneity assessment, the Tukey HSD test was used to determine the difference between homogeneous groups, and the Tamhane T2 test was used in non-homogeneous groups.
1: Who wants body weight gain; 0: Who is satisfied with their body image; -1:Who wants body weight loss.
*Different letters indicate statistical differences.

Body image perception reflects how the individual wants to see themselves in their mind. In cases where there is dissatisfaction with body image, eating behavior disorders are reported to occur in individuals[28]. A study emphasized that body image satisfaction decreased as weight increased, and individuals with unhealthy diets were less satisfied with their bodies[29]. In another study, it has been reported that individuals with high body weight tend to have more negative emotional intensity and more emotional eating compared to individuals with normal and low body weight[30]. In the present study, the rate of those who were satisfied with their body image was 23.8%. In this study, the total score of the emotional eating scale was higher in those who wanted to lose body weight than those who tried to gain weight. This may be due to the relationship between the reason for weight gain and food choice; it has been reported that individuals consume more high-fat and high-carbohydrate foods to cope with their emotional state[12]. This relationship between body perception and picky eating may be associated with individuals' eating behavior. In this study, no difference was observed in the APEQ total score and subgroups except for the subscale of mealtime avoidance of APEQ according to body perception. Although PE and disordered eating outcomes are positively related[31], childhood PE is associated with a lower frequency of intake of a variety of healthy foods among young adults[32] but may not be related to body perception.

Picky eating behavior is a behavior that can lead to symptoms of the eating disorder ARFID and has been reported to cause body weight loss[6]. The relationship between PE and body weight is not clear in the literature. While PE was associated with being underweight in some studies[32,33], Finistrella et al.[34] in the present study, it was associated with being overweight. In this study, picky eating scores were higher in pre-obese and

obese individuals compared to those with normal body weight. This suggests that the increase in PE behavior is associated with a decrease in fruit and vegetable consumption[35,36] and may be due to a negative impact on psychosocial and emotional states such as depression and stress[26,27,31]. This suggests that there may be an increase in picky eating behavior in obese people because changes in mood trigger emotional eating, and emotional eating behavior is often associated with obesity[7,8].

It is reported that emotional eating is an essential factor in body weight gain, and 60% or more of obese individuals are emotional eaters[37]. Emotional eaters are less aware of intrinsic hunger and satiety cues. This is thought to be partly because emotional eating is associated with stress that alters awareness of these internal cues[38]. More than 40% of the participants had a BMI above 25, and 76.2% were dissatisfied with their body image. Similarly, in this study, emotional eating was higher in pre-obese and obese individuals than in lean individuals ($p < 0.05$). It is thought that the evaluation of picky eating behavior, emotional eating behavior, and psychological conditions such as depression, stress and anxiety together will contribute to the literature.

To our knowledge, this is the first investigation into how emotional eating, picky eating, and body image are related. Body image dissatisfaction and emotional eating are reported to be associated with various eating behavior disorders such as bulimia, binge eating, and compulsive eating[39]. To deal with body dissatisfaction, intuitive eating is advised. This is described as having a deep connection with one's internal hunger and satiety signals and eating in response to these signals[40]. However, reduction of emotional eating symptoms has been suggested to address body image dissatisfaction[41].

Conclusion

This study linked emotional eating and body image assessment, whereas picky eating and emotional eating were not. Data on the relationship between body image perception, emotional eating, and picky eating are limited. This study examined the relationship between body image perception, emotional eating, and picky eating in individuals without chronic diseases. It was found that body image dissatisfaction was associated with emotional eating and its sub-dimensions. Considering that body image dissatisfaction may cause many eating behavior disorders, it is thought that regulation of body perception will contribute to the prevention of eating behavior disorders.

Although picky eating behavior is thought to occur mostly in children, it is increasingly prevalent in adults. In addition, picky eating behavior is associated with body weight, quality of life, and mood disorders such as depression, anxiety, and stress. Evaluation of PE status in individuals during childhood may prevent PE in adulthood positively.

In conclusion, PE is associated with emotional eating, body weight, and body perception. It is thought that there is a need to evaluate depression, anxiety, stress, and quality of life parameters in future face-to-face studies.

Limitations

This is the first study to evaluate the relationship between body image perception, emotional eating, and picky eating. In addition, the fact that the participants were conducted with healthy individuals is among its strengths to avoid any other confounding factor. Nevertheless, the study has a few limitations. Firstly, evaluating depression, anxiety, and stress in the study with data assessing the emotional states of the participants could have had a positive effect in terms of determining the emotional states of the participants. Secondly, examining the quality of life in the study could have been associated with picky eating behavior. Finally, the study's limitations include that body weight and height were taken to identify the individuals in the study.

Ethics Approval

The Social and Human Sciences Research Ethics Committee of Tokat Gaziosmanpaşa University granted clearance for the study in session number 15 and decision number 01-56 on 07/12/2022.

Conflict of Interests

There are no conflicts of interest between the writers.

Acknowledgments

We want to thank all the participants in the study.

References

1. Zwierczyk U, Sowada C, Duplaga M. Eating Choices —The Roles of Motivation and Health Literacy: A Cross-Sectional Study. Nutrients. 2022;14(19):4026.
2. Jackson SE, Llewellyn CH, Smith L. The obesity epidemic-Nature via nurture: A narrative review of high-income countries. SAGE open medicine. 2020;8:2050312120918265.
3. Taylor CM, Wernimont SM, Northstone K, Emmett PM. Picky/fussy eating in children: Review of definitions, assessment, prevalence, and dietary intakes. Appetite. 2015;95:349–59.
4. Zickgraf HF, Franklin ME, Rozin P. Adult picky eaters with symptoms of avoidant/restrictive food intake disorder: comparable distress and comorbidity but different eating behaviors compared to those with disordered eating symptoms. J Eat Disord. 2016;4:26.
5. Galloway AT, Fiorito L, Lee Y, Birch LL. Parental pressure, dietary patterns, and weight status among girls who are "picky eaters". J Am Diet Assoc. 2005;105(4):541–8.
6. Ellis JM, Galloway AT, Webb RM, Martz DM. Measuring adult picky eating: The development of a multidimensional self-report instrument. Psychol Assess. 2017;29(8):955.
7. Fox G, Coulthard H, Williamson I, Aldridge V. How multiple threats to safety affects quality of life for picky eating adults: A new explanatory model. Appetite. 2023;181:106396.
8. Association AP. American Psychiatric Association-Diagnostic And Statistical Manual of Mentale Disorders, (DMS-V). (V). Arlington: American Psychiatric Association Publishing. 2013.
9. Stark ML, Katariina. Emotional eating and eating disorder psychopathology. J Eat Disord. 2001;9(3):251–9.
10. Annesi JJ. Psychosocial predictors of decay in healthy eating and physical activity improvements in obese women regaining lost weight: translation of behavioral theory into treatment suggestions. Trans Behav Med. 2016;6(2):169–78.
11. Song Y-M, Lee K, Sung J. Genetic and environmental relationships between eating behavior and symptoms of anxiety and depression. Eat Weight Disord. 2019;24:887–95.
12. Gibson EL. Emotional influences on food choice: sensory, physiological and psychological pathways. Physiol Behav. 2006;89(1):53–61.
13. Macht M. How emotions affect eating: A five-way model. Appetite. 2008;50(1):1–11.
14. Devonport TJ, Nicholls W, Fullerton C. A systematic review of the association between emotions and eating behaviour in normal and overweight adult populations. J Health Psychol. 2019;24(1):3–24.
15. Ayyıldız F, Akbulut G, Ermumcu MŞK, Tek NA. Emotional and intuitive eating: an emerging approach to eating behaviours related to obesity. J Nutr Sci. 2023;12:e19.
16. Sarwer DB, Thompson JK, Cash TF. Body image and obesity in adulthood. Psychiatr Clin. 2005;28(1):69–87.
17. Cash TF, Jakatdar TA, Williams EF. The Body Image Quality of Life Inventory: Further validation with college men and women. Body Image. 2004;1(3):279–87.
18. Cakmur H, Anuk T. Frequency awareness and management of obesity among health care providers. Acta Medica Mediterr. 2017;33:1073–9.
19. Menghi L, Endrizzi I, Cliceri D, Zampini M, Giacalone D, Gasperi F. Validating the Italian version of the Adult Picky Eating Questionnaire. Food Qual Prefer. 2022;101:104647.
20. Stunkard A, Sorensen T, Schulsinger F, Kety S, Rowland L, Sidman R, et al. Use of theDanish Adoption Register for the study of obesity and thinness. Raven Press New York;1983. p. 115–20.
21. Ayyildiz F, Esin K. Validity and reliability of the Turkish version of the adult picky eating questionnaire. Prog Nutr. 2022;24(3).
22. Garaulet M, Canteras M, Morales E, López-Guimerà G, Sánchez-Carracedo D, Corbalán-Tutau M. Validation of a questionnaire on emotional eating for use in cases of obesity;the Emotional Eater Questionnaire (EEQ). Nutr Hosp. 2012;27(2):645–51.
23. Arslantaş H, Dereboy F, Yüksel R, İnalkaç S. Duygusal yeme ölçeği'nin türkçe çevirisinin geçerlik ve güvenirlik çalışması. Türk Psikiyatri Dergisi. 2019;30:1–10.
24. Organization WH. Obesity: preventing and managing the global epidemic: report of a WHO consultation. 2000.
25. Fox G, Coulthard H, Williamson I, Wallis D. "It's always on the safe list": Investigating experiential accounts of picky eating adults. Appetite. 2018;130:1–10.
26. Kauer J, Pelchat ML, Rozin P, Zickgraf HF. Adult picky eating. Phenomenology, taste sensitivity, and psychological correlates. Appetite. 2015;90:219–28.
27. Wildes JE, Zucker NL, Marcus MD. Picky eating in adults: Results of a web-based survey. Int J Eat Disord. 2012;45(4):575–82.
28. Mond J, Van den Berg P, Boutelle K, Hannan P, Neumark-Sztainer D. Obesity, body dissatisfaction, and emotional well-being in early and late adolescence: findings from the project EAT study. J Adolesc Health. 2011;48(4):373–8.
29. Grogan S, Rothery L, Cole J, Hall M. Posting selfies and body image in young adult women: The selfie paradox. Soc Media. 2018;7(1):15–36.
30. Geliebter A, Aversa A. Emotional eating in overweight, normal weight, and underweight individuals. Eat Behav. 2003;3(4):341–7.
31. Barnhart WR, Hamilton L, Jordan AK, Pratt M, Musher-Eizenman DR. The interaction of negative psychological well-being and picky eating in relation to disordered eating in undergraduate students. Eat Behav. 2021;40:101476.
32. Dubois L, Farmer A, Girard M, Peterson K, Tatone-Tokuda F. Problem eating behaviors related to social factors and body weight in preschool children: A longitudinal study. Int J Behav Nutr Phys Act. 2007;4(1):1–10.
33. Ekstein S, Laniado D, Glick B. Does picky eating affect weight-for-length measurements in young children? Clin Pediat. 2010;49(3):217–20.
34. Finistrella V, Manco M, Ferrara A, Rustico C, Presaghi F, Morino G. Cross-sectional exploration of maternal reports of food neophobia and pickiness in preschooler-mother dyads. J Am Coll Nutr. 2012;31(3):152–9.
35. Cole NC, An R, Lee S-Y, Donovan SM. Correlates of picky eating and food neophobia in young children: a systematic review and meta-analysis. Nutr Rev. 2017;75(7):516–32.
36. Pereboom J, Thijs C, Eussen S, Mommers M, Gubbels JS. Association of picky eating around age 4 with dietary intake and weight status in early adulthood: A 14-year follow-up based on the KOALA birth cohort study. Appetite. 2023;188:106762.
37. Ganley RM. Emotion and eating in obesity: A review of the literature. Int J Eat Disord. 1989;8(3):343–61.
38. Tan CC, Chow CM. Stress and emotional eating: The mediating role of eating dysregulation. Pers Individ Differ. 2014;66:1–4.
39. Van Strien T, Engels RC, Van Leeuwe J, Snoek HM. The Stice model of overeating: tests in clinical and non-clinical samples. Appetite. 2005;45(3):205–13.
40. Tylka TL. Development and psychometric evaluation of a measure of intuitive eating. J Couns Psychol. 2006;53(2):226.
41. Fairburn CG. Cognitive behavior therapy and eating disorders: Guilford Press;2008.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Methylation of GLUT5 and Electromotile Responses During Chronic and Acute Sodium Salicylate Administration in the Cochlear Outer Hair Cells

Koklear Dış Tüy Hücrelerine Kronik ve Akut Sodyum Salisilat Uygulamasına GLUT5 Metilasyon ve Elektromotil Yanıtlar

Mustafa Yildiz[1], Metin Budak[1,3], Zuleyha Dilek Gulmez[2], Erdogan Bulut[3]

[1]Department of Biophysics, Faculty of Medicine, Trakya University, Edirne; [2]Department of Audiology, Faculty of Health Sciences, Istanbul University-Cerrahpasa, Istanbul; [3]Mirko TOS Ear and Hearing Center, Trakya University, Edirne, Türkiye

ABSTRACT

Aim: *Prestin molecule and transporter fructose GLUT5 in the lateral walls of outer hair cells are essential. This study aimed to investigate epigenetic alterations in the GLUT5 gene.*

Materials and methods: *The animals were divided into three groups randomly. No injection was received in the first group (n=3). Groups 2(n=3) and 3(n=6) were injected with intramuscular saline and sodium salicylate, respectively. Electrophysiological measurements were performed at 1st, 2nd, and 8th hours to evaluate the acute effect and in 2 weeks to evaluate the chronic effect. Methylation of CpG dinucleotides in the promoter can lead to dysregulated and repressed gene expression. Genomic DNA was isolated from bone tissues, treated with bisulfite, and analyzed using methylation specific PCR (polymerase chain reaction) (MSP). Epigenetic alterations in the GLUT5 gene were investigated by using the MSP method.*

Results: *There was a significant decrease in electrophysiological measurements at all frequencies in the acute effect ($p<0.01$), whereas there was no significant difference in the chronic effect for Group 3 ($p>0.05$). However, methylation of GLUT5 was observed to be increased during acute administration, followed by a decreasing trend to normal during the chronic period.*

Conclusion: *Our findings show that methylation of GLUT5 may decrease GLUT5 expression in lateral walls of outer hair cells, thereby changing prestin-bound fructose transport in cell membranes due to reduced GLUT5 expression.*

Keywords: *GLUT5; outer hair cells; cochlea; distortion product otoacoustic emissions; sodium salicylate*

ÖZET

Amaç: *Prestin molekülü ve taşıyıcı fruktoz GLUT5 dış tüy hücrelerinin lateral duvarlarında önemli bir parçasıdır. Bu çalışma GLUT5 genindeki epigenetik değişiklikleri araştırmayı amaçlamıştır.*

Materyal ve Metot: *Hayvanlar rastgele üç gruba ayrıldı. Birinci gruba enjeksiyon yapılmadı (n=3). Grup 2 (n=3) ve 3 (n=6)'e sırasıyla kas içi salin ve sodyum salisilat enjekte edildi. Elektrofizyolojik ölçümler akut etkiyi değerlendirmek için 1., 2. ve 8. saatlerde ve kronik etkiyi değerlendirmek için 2. haftada gerçekleştirilmiştir. GLUT5 genindeki epigenetik değişiklikler Metilasyon spesifik PCR yöntemi kullanılarak araştırıldı.*

Bulgular: *Akut etkide tüm frekanslarda elektrofizyolojik ölçümlerde anlamlı bir azalma görülürken ($p<0,01$), kronik etkide Grup 3 için anlamlı bir fark yoktu ($p>0,05$). Bununla birlikte, GLUT5 metilasyonunun akut uygulama sırasında arttığı ve ardından kronik dönemle birlikte normale dönme eğiliminde olduğu gözlenmiştir.*

Sonuç: *Bulgularımız GLUT5 metilasyonunun dış tüy hücrelerinin lateral duvarlarında GLUT5 ekspresyonunu azaltabileceğini ve böylece GLUT5 ekspresyonunun azalmasına bağlı olarak hücre membranında prestine bağlı fruktoz taşınımını değiştirebileceğini göstermektedir.*

Anahtar kelimeler: *GLUT5; dış tüy hücreleri; koklea; distorsiyon ürünü otoakustik emisyonlar; sodyum salisilat*

İletişim/Contact: *Mustafa Yildiz, Department of Biophysics, Faculty of Medicine, Trakya University, 22030 Edirne, Türkiye* • ***Tel:*** *0284 235 76 41* • ***E-mail:*** *myildiz@live.com* • ***Geliş/Received:*** *06.10.2023* • ***Kabul/Accepted:*** *27.03.2024*

ORCID: *Mustafa Yıldız: 0000-0002-1192-6242 • Metin Budak: 0000-0002-5968-2048 • Züleyha Dilek Gülmez: 0000-0001-8387-4181 • Erdoğan Bulut: 0000-0003-2036-6870*

Kafkas J Med Sci 2024; 14(1):72–79
doi: 10.5505/kjms.2024.95870

Introduction

The mammalian cochlea is anatomically located within the organ of Corti and consists of two types of hair cells. The cochlea contains two types of hair cells: inner and outer hair cells[1]. These cells have different functions. While acoustic information is transferred to auditory nerve fibers via the electrical signals of inner hair cells (IHCs), outer hair cells (OHCs) enhance the stimulus mechanically by increasing vibrations of the cochlear division[2]. OHCs are known to amplify the vibration of the basilar membrane with a pattern often referred to as the traveling wave or cochlear amplification. One of their unique characteristics is their ability to alter their length in response to changes in membrane potential, known as electromotility[3]. Prestin is a transmembrane motor protein located on the lateral wall of OHCs[4]. Prestin is essential for the cochlear amplification process, electromotile responses and sharp frequency tuning[5,6]. GLUT5 (Glucose transporter type 5) is a fructose-specific transporter, which is reported to be abundantly expressed in the OHC lateral wall and was initially suggested as the OHC motor protein[7]. It has been shown that GLUT5 is not needed for OHC electromotility and cochlear amplification[8]. The discovery of prestin has become an academic interest concerning sugar transport in OHCs[1,9] as sugar transport is closely related to the response of OHC electromotility[10–12].

Cytoplasmic anions (predominantly Cl-) are utilized by prestin as an extrinsic voltage sensor and mediate changes responding to changes in OHC membrane potential[4]. By binding to prestin, these anions increase their affinity and move intracellularly with alteration in membrane voltage and simultaneous depolarization of OHCs, resulting in cell length shortening. In contrast, during hyperpolarization, they move towards the extracellular region, leading to increased length of the cells[4,5]. Suppose the cytoplasm does not have any monovalent anions. In that case, the shortened OHC length is maintained in maximum contraction because of the prestin molecules[5]. In addition, the blocking effect of salicylate on prestin is a well-known phenomenon in auditory physiology. Salicylate can also affect the physical properties of the stereocilia bundle by reducing bending stiffness[13,14]. When OHCs become damaged or dysfunctional due to excessive aspirin intake, this leads to decreased sensitivity in our ears and, eventually, hearing loss if left untreated[14–16].

Epigenetics is heritable gene expression modifications that occur without changes in the primary DNA sequence[17]. Recent studies investigating the effect of age, developmental variables and environmental variables (stress, etc.) on base sequences have demonstrated gene silencing by adding methyl groups through enzymatic mechanisms in DNA molecules in carcinogenesis and tumorigenesis. At the same time, demethylation was associated with gene activation[18–21]. This study aimed to investigate epigenetic alterations in the GLUT5 gene.

Materials and Methods

Animals

All animals were subjected to Bilateral otoscopic and audiological assessments, including 1-kHz high-frequency DPOAE and tympanometry tests. The tympanometry and DPOAE measurements were used to determine Otoacoustic Emissions (OAE) (Madsen Capella-Denmark/GN Otometrics A/S). The probe device was placed in the ear canal and stationary with measuring equipment. Animals have been placed in a soundproof room. All measurements were performed using sodium pentobarbital (40 mg/kg) when the guinea pigs were put under general anesthesia with a warming blanket, and the body temperature was maintained at 38°C.

Treatment Protocol

Twelve animals (n=24 ears) with normal electrophysiological results were randomly stratified into three groups: Group 1 was the control group, Group 2 was the placebo control, and Group 3 was the sodium salicylate group. The guinea pigs in Group 1 (negative control group, n=6 ears) received no drug. Group 2 (positive control group, n=6 ears) received physiological saline (NaCl 0.9%) at a dose of 200 mg/kg/day twice daily by subcutaneous injection for two weeks. Group 3 (experimental group, n=12 ears) received salicylate at 200 mg/kg/day twice daily by subcutaneous injection for two weeks[22,23]. Electrophysiological measurements to confirm the chronic effect[24] were performed immediately before sodium salicylate injection (Day 0), and at the end of 2 weeks, DPOAE measurements were performed 1 hour before and 2–8 hours after the injections to adjust the acute results. After electrophysiological recordings, all animals were sacrificed under 200 mg/kg sodium pentobarbital (high-dose anesthesia), followed by dissection of the temporal bones for DNA purification to assess the acute (0 to 8 hours) and chronic (8 hours

to 2 weeks) effects of salicylate administration[21,24]. The possible methylations in the promoter of the GLUT5 gene were evaluated by MSP. Freshly dissolved 200 mg/kg sodium salicylate from Sigma (St. Sigma-Aldrich; Germany) was administered intramuscularly twice-daily injections for two weeks[22,23,25–27].

Electrophysiological Recordings

The acoustic stimulation tones referred to as primary frequencies were f1 and f2. L1 and L2 as primary levels were adjusted individually, and the frequency ratio f2/f1 was fixed at 1.22. Stimulant degrees were fixed at 65- and 55-dB sound pressure levels (SPL) for L1 and L2, respectively. Several essential aspects were evaluated when generating DPOAE results between 0.75 and 8 kHz with 2f1-f2 mode. The duration of the test was 60 seconds. The amplitude at least 3 dB higher than the mean background noise level sampled in various frequencies surrounding the emission frequency is a widely accepted criterion for detecting and confirming DPOAE. S/N-R (frequency-specific signal/noise ratios) was evaluated in both ears of the experimental animals (guinea pigs)[24].

Genomic DNA Isolation

The temporal bones were frozen in liquid nitrogen and then shattered, and otic capsules were exposed and resected. These processes were performed in a separate porcelain bowl to prevent contamination of sample DNA and DNA from other tissues. The GeneMATRIX DNA (Cat No. 220342, Eurx, Poland) kit was used to isolate DNA from the resected otic capsules according to manufacturer specifications.

Methylation Specific Polymerase Chain Reaction

Methylation-specific PCR (MSP) is the most widely used tool for qualitative DNA methylation analysis, and it has many advantages, such as simplicity of design and implementation and sensitivity in detecting small amounts of methylated and aberrant DNA. Bisulfite conversion is a common approach for DNA methylation analysis in gene-specific analysis studies. By treating DNA with bisulfite, cytosine is converted to uracil. At the same time, 5-methylcytosine remains intact, providing information on methylated regions of DNA, even with a single nucleotide change. The MSP is a PCR-based method routinely used for gene-specific DNA methylation analysis after bisulfite treatment. DNA concentration and quantification were determined at 260/280 nm with Nano-200 nucleic acid analyzer spectrophotometry. Next, 10 µL of DNA was taken from each sample. Bisulfite treatment was done according to the EpiJET Bisulfite Conversion Kit (K1461, Thermo Fisher Scientific, USA) and followed the manufacturer's recommendations. This treatment transforms non-methylated cytosines to thymine but does not convert methylated cytosines. The CpG sequences in the promoter-exon1 connection of the GLUT5 gene were identified using MethPrimer 2.0 to change the region[27]. Methylation-specific PCR was carried out using the following protocols:

Polymerase chain reaction conditions for the methylated and unmethylated residues (Fig. 1):

Polymerase chain reaction primers for promoter-exon1 linkage zone of GLUT5 (SLC2A5),

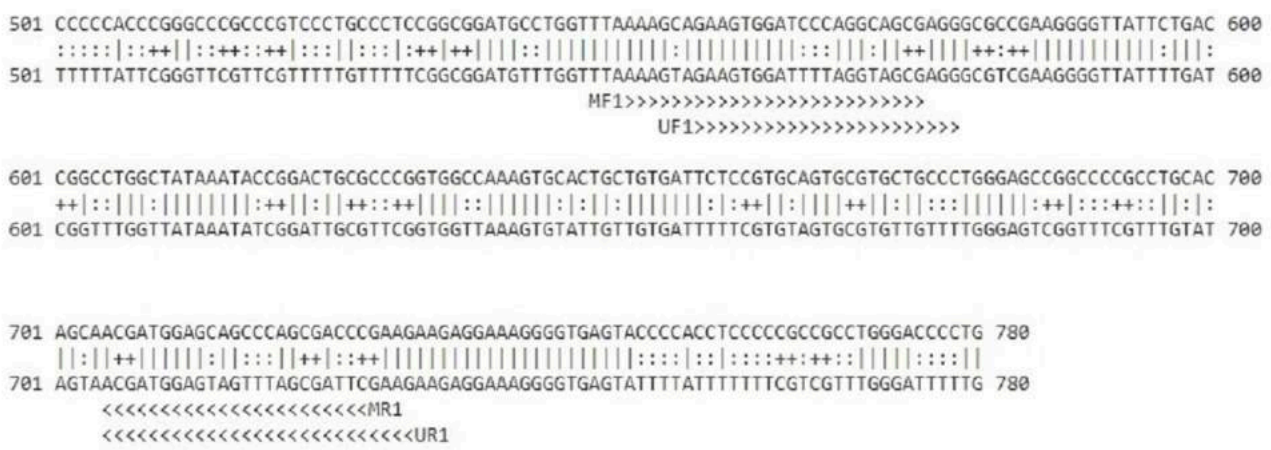

Figure 1. *GLUT5 methylated and unmethylated primers in original sequence.*

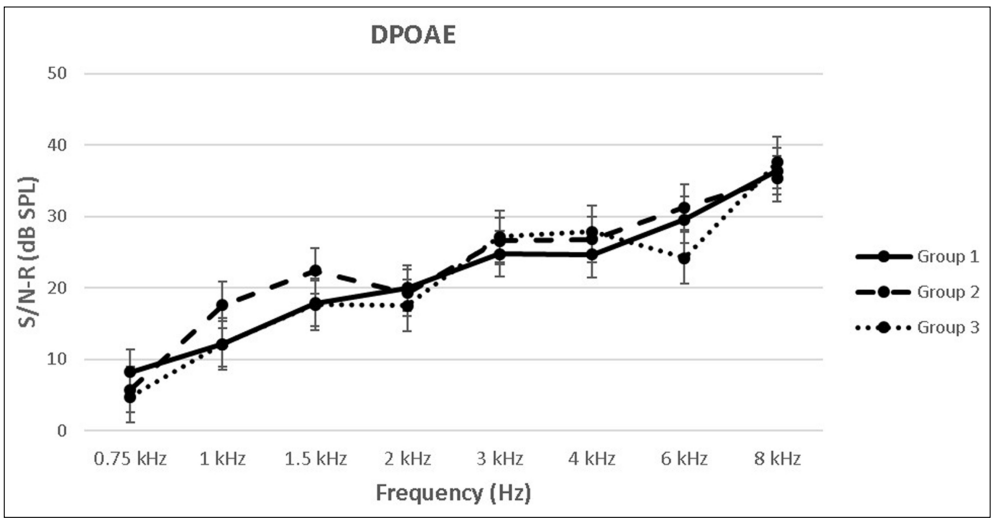

Figure 2. *Mean baseline S/N-R values in all groups.*

MetForward:
AAAGTAGAAGTGGATTTTAGGTAGCG-3'

MetReverse:
CAATACACTTTAACCACCGAAC, PCR product: 99 bp,

UnMetForward:
GAAGTGGATTTTAGGTAGTGAGG,

UnMetReverse:
CACAACAATACACTTTAACCACCA, PCR product: 98 bp.

Polymerase Chain Reaction Conditions and Agarose Gel Imaging

The buffer of PCR 1x, $MgCl_2$ (Thermo Fisher Scientific) and, two mM, Dimethylsulfoxide (DMSO): 5% (v/v) (Thermo Fisher Scientific) and, dNTP: 1.25 mM (Thermo Fisher Scientific) and, M/U Primer Forward: 10 pmol, M/U Primer Reverse: 10 pmol, Taq Polymerase: 1U (5U/μL) (Thermo Fisher Scientific) and sample DNA: 100 ng and dH_2O was used to reach a minimum of 20 μL and the conditions for PCR were as follows: 94°C 10'initiation, 94°C 40", 55°C 35", 72°C 35" 40 cycles, 72°C 7'ending.

All PCR products were spotted with EtBr (Thermo Fisher Scientific) on 2.5% agarose gel, and bands according to their pixel densities were evaluated using MiniBIS DNR Gel Analyzer[24,28].

Statistical Analysis

Statistical analyses were performed after checking the standard normal distribution of data (IBM Statistical Package for Social Sciences (SPSS) program version 19 for Windows; IBM Inc., Chicago, IL, USA). Since the data are unsuitable for parametric tests, intragroup comparisons were tested using the Wilcoxon test, and intergroup comparisons were made using the Mann-Whitney U test. The Kruskal-Wallis test was applied when more than two groups were involved in intergroup comparisons. Graphical results were plotted as mean ±1 standard error of the mean for each group.

Results

We evaluated the effect of sodium salicylate on the electromotive responses of OHCs using the S/N-R parameters in DPOAE measurements using the 2f1-f2 mode. During initial measurements ($p>0.05$), there was no statistical difference between the groups' DPOAE S / N-R responses. S / N-R values were above 3 dB at all frequency levels in the control group for DPOAE tests. An increase in S/N-R values was noted from low frequency to high frequency due to the mobility of OHCs in the cochlea (Fig. 2). Error bars represent one standard error of the mean and are plotted for Group 1, Group 2 and Group 3. They were comparable across all three groups.

There was no statistically significant difference in DPOAE S/N-R responses between 0.75 kHz and 8 kHz in Group 2 ($p>0.05$) (Fig. 3). Error bars represent one standard error of the mean and are plotted for the control and the other groups. They were comparable across all three groups. In Group 3, a statistically significant decrease was detected in DPOAE S/N-R responses starting at 1 hour ($p<0.01$), indicating the acute effect of sodium salicylate (Fig. 4) and a

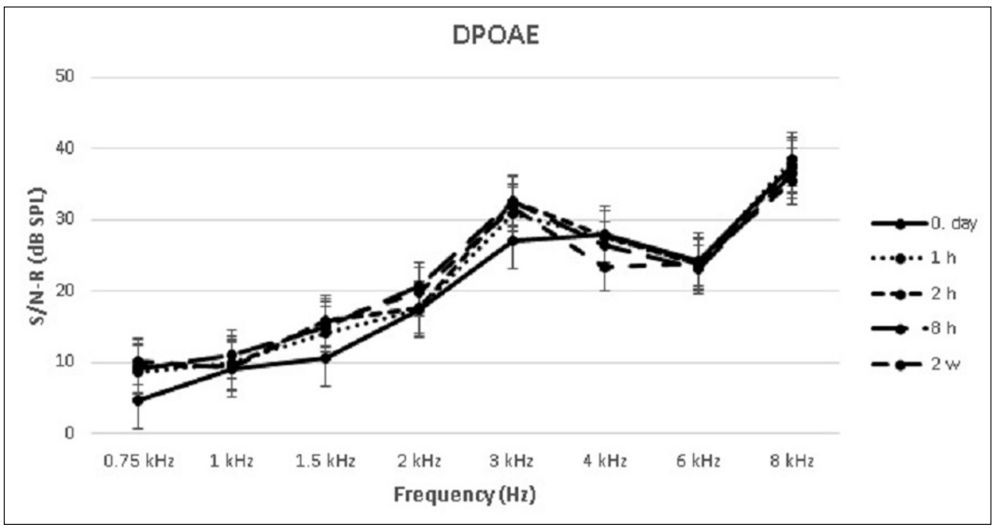

Figure 3. *S/N-R values during sodium salicylate medication administered to guinea pigs in Group 2. The figure depicts changes in DPOAEs during acute (1 hour and 8 hours) and chronic (8 hours to 2 weeks) periods.*

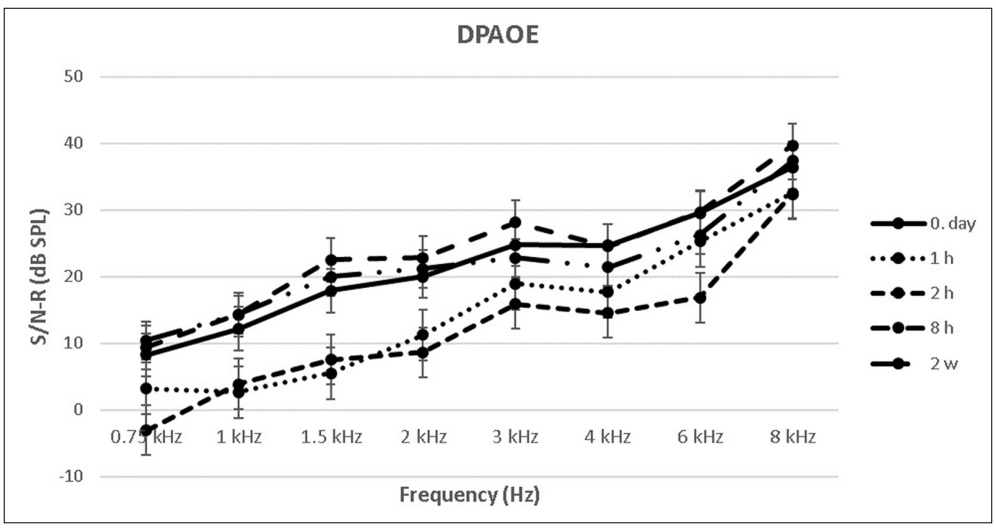

Figure 4. *S/N-R values during sodium salicylate medication administered to guinea pigs in Group 3. The figure depicts changes in DPOAEs during acute (1 hour and 8 hours) and chronic (8 hours to 2 weeks) periods.*

statistically significant decrease in DPOAE S / N-R responses ($p<0.01$) occurred at 2 hours after sodium salicylate injection; however, those changes were observed to return to baseline at 8 hours. Comparison of Group 1 and Group 3 during sodium salicylate administration showed a statistically significant decrease in DPOAE S/N-R responses in Group 1 ($p<0.01$). In contrast, this important difference was not observed at 8 hours ($p>0.05$).

There was a substantial increase in DPOAE S/N-R response ($p>0.05$). However, long-term salicylate administration's differences were insignificant (Fig. s 3 and 4). Starting from 8 hours, the increase and the DPOAE S/N-R responses declined to baseline values within two weeks. Figure 3 shows no statistically significant difference between the DPOAE S / N-R responses at Group 2 frequencies ($p>0.05$). There is no statistically significant difference between Group 2 and Group 1 ($p>0.05$) at any of the frequencies during long-term sodium salicylate administration.

The present research investigated GLUT5 gene promoter methylation in cochlear DNA from guinea pigs via a methylation-specific polymerase chain reaction. No methylation was observed in the GLUT5 gene promoter at 2 hours after acute salicylate administration in Group 1 and Group 2 (Fig. 5). However, significant

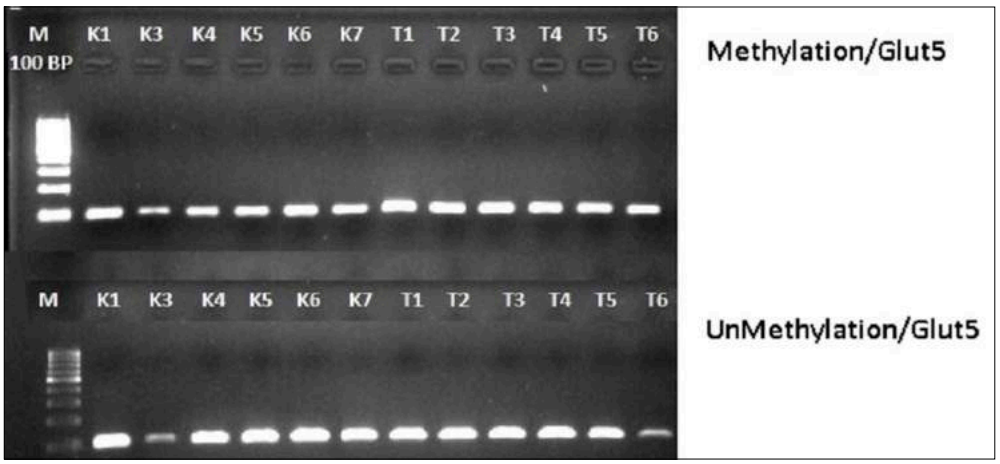

Figure 5. *Polymerase chain reaction shows increased methylation at 2 hours after sodium salicylate administration (T1–T6:Group 3). No methylation was observed in the GLUT5 gene sequence on DNA as the acute effect at 2 hours in Group 1 (K1–K4) and Group 2 (K4–K7).*

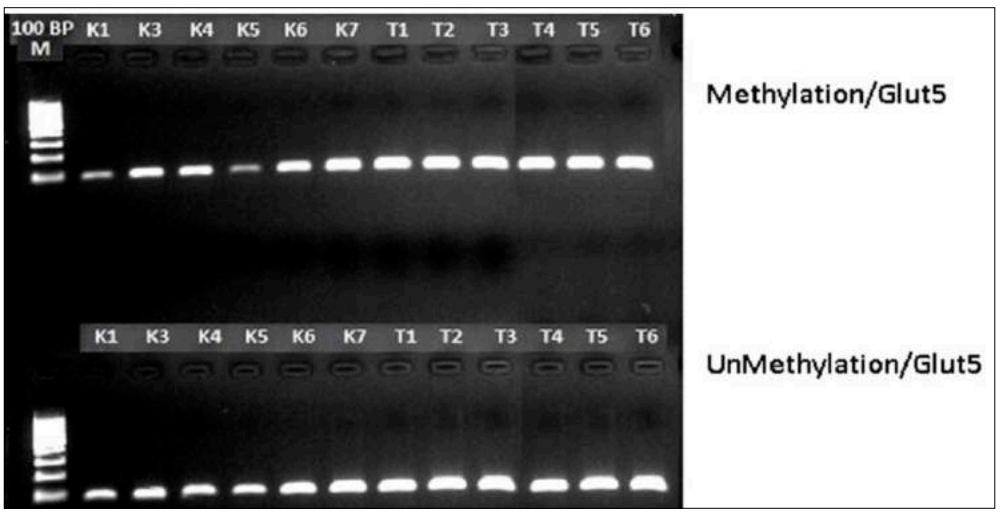

Figure 6. *Polymerase chain reaction results in all groups at two weeks (K1–K4:Group 1; K4–K7:Group 2; T1–T6:Group 3). No methylation was observed in the GLUT5 gene sequence on DNA, as the chronic effect was two weeks in any of the groups.*

methylation was observed with acute administration in Group 3 (Fig. 5). On the other hand, there was no methylation in the GLUT5 gene with chronic sodium salicylate administration (Fig. 6). In chronic salicylate administration, GLUT5 was shown to be unmethylated, showing the potential activity in the GLUT5 gene. Significant methylation was observed in the GLUT5 gene on DNA as the acute effect (Figure 5); however, a chronic effect on DNA was not observed in the same gene during sodium long-term salicylate administrations (Figure 6). Whereas DNA unmethylation of the region revealed the activated GLUT5 gene, DNA was not methylated in GLUT5 gene Group 1 and Group 2 (Fig. 6) under the effect of chronic salicylate administration at two weeks.

Discussion

Several studies have shown that age, developmental, and environmental factors (e.g., stress) may cause gene silencing by methylation of nucleotide sequences[29]. While this appears to cause only chemical changes in DNA by methylation/demethylation under the circumstances, it has also been correlated with gene activation/inhibition, for example, carcinogenesis. Salicylates are well-known ototoxic agents[24–27]. The acute effect of a single-dose salicylate injection reversibly reduces the mobility of outer hair cells. In contrast, chronic salicylate administration increases neuronal activity, often causing reversible hearing loss and tinnitus[25].

As a membrane protein, prestin can selectively transport the sugar molecule[4] on the lateral wall of OHCs. Salicylates can affect GLUT5[1], as well as affect sugar transport in guinea pig OHCs[19]. In recent studies, decreased DPOAE values were observed in the cochlea's outer hair cells under the acute effect of a single salicylate injection, while these values are back to baseline with chronic administration. In the present study, S/N-R levels in DPOAE measurements were significantly reduced when 200 mg/kg sodium salicylate was administered acutely by subcutaneous injection[30]. Studies on prestin have reported a potential hearing loss and decreased DPOAE responses in prestin-knockout experimental animals[5,24,26].

Sodium salicylate is known to block the OHC electromotility response[15]. Prestin acts as an extrinsic voltage sensor by binding Cl ions. Acting as an antagonist and competing with Cl ions, sodium salicylate competitively binds to the Cl-binding sites of prestin, by inhibiting OHC electromotility[13]. However, during long-term administration of sodium salicylate, S/N-R values significantly increase in DPOAE measurements. Salicylate binding to the Cl-binding sites of prestin has been found to have an acute effect on outer hair cells (OHCs), leading to their inactivation. This is because salicylates bind strongly with chloride ions, which are necessary for OHCs' normal functioning. Our findings show long-term salicylate administration may alter chloride ion concentrations and increase electromotile OHC responses. We think GLUT5 methylation during the acute effect of salicylate administration may block GLUT5 expression. As shown in our previous study[24], the decrease in DPOAE recordings during the acute effect suggests a possible association with the blockade of prestin.

Conclusion

Our current results have shown that salicylate administration may increase the methylation of GLUT5 during acute administration but return to baseline levels with chronic administration. This study suggests that epigenetic regulation of fructose transport may be prestin-dependent. Consequently, prestin-mediated transport of fructose may be associated with OHC electromotility.

The main result of this study is the methylation observed in the GLUT5 gene, which is a fructose transporter, under the acute effect of salicylate administration, and methylation of GLUT5 returned to baseline levels during chronic administration.

Ethics Approval

In this study, we used 12 healthy young or adult pigmented Cavia porcellus (Guinea pigs) with auropalpebral reflexes (weight range, 200–320 g) upon obtaining the approval of the Animal Care and Use Committee of the University on October 6, 2015.

References

1. Ashmore J. Cochlear outer hair cell motility. Physiol Rev. 2008;88(1):173–210.
2. Fettiplace R. Hair cell transduction, tuning, and synaptic transmission in the mammalian cochlea. Comprehensive Physiology. 2011;7(4):1197–227.
3. Kachar B, Brownell WE, Altschuler R, Fex J. Electrokinetic shape changes of cochlear outer hair cells. Nature. 1986;322(6077):365–8.
4. Zheng J, Shen W, He DZ, Long KB, Madison LD, Dallos P. Prestin is the motor protein of cochlear outer hair cells. Nature. 2000;405(6783):149–55.
5. Dallos P, Wu X, Cheatham MA, Gao J, Zheng J, Anderson CT, et al. Prestin-based outer hair cell motility is necessary for mammalian cochlear amplification. Neuron. 2008;58(3):333–9.
6. Bai JP, Navaratnam D, Santos-Sacchi J. Prestin kinetics and corresponding frequency dependence augment during early development of the outer hair cell within the mouse organ of Corti. Sci Rep. 2019;9(1):16460.
7. Nakazawa K, Spicer SS, Schulte BA. Postnatal expression of the facilitated glucose transporter, GLUT 5, in gerbil outer hair cells. Hear Res. 1995;82(1):93–9.
8. Wu X, Wang X, Gao J, Yu Y, Jia S, Zheng J, et al. Glucose transporter 5 is undetectable in outer hair cells and does not contribute to cochlear amplification. Brain Res. 2008;1210:20–8.
9. Parham K, Sohal M, Petremann M, Romanet C, Broussy A, Tran Van Ba C, et al. Noise-induced trauma produces a temporal pattern of change in blood levels of the outer hair cell biomarker prestin. Hear Res. 2019;371:98–104.
10. Wu X, Currall B, Yamashita T, Parker LL, Hallworth R, Zuo J. Prestin-prestin and prestin-GLUT5 interactions in HEK293T cells. Dev Neurobiol. 2007;67(4):483–97.
11. Matsuoka K, Wada K, Miyasaka Y, Yasuda SP, Seki Y, Nishito Y, et al. OHC-TRECK. A Novel System Using a Mouse Model for Investigation of the Molecular Mechanisms Associated with Outer Hair Cell Death in the Inner Ear. Sci Rep. 2019;9(1):5285.
12. Yang K, Huang ZW, Liu ZQ, Xiao BK, Peng JH. Long-term administration of salicylate enhances prestin expression in rat cochlea. Int J Audiol. 2009;48(1):18–23.

13. Oliver D, He DZ, Klocker N, Ludwig J, Schulte U, Waldegger S, et al. Intracellular anions as the voltage sensor of prestin, the outer hair cell motor protein. Science. 2001;292(5525):2340–3.
14. Hakizimana P, Fridberger A. Effects of salicylate on sound-evoked outer hair cell stereocilia deflections. Pflugers Arch. 2015;467(9):2021–9.
15. Tunstall MJ, Gale JE, Ashmore JF. Action of salicylate on membrane capacitance of outer hair cells from the guinea-pig cochlea. J Physiol. 1995;485(Pt 3)(3):739–52.
16. Chen B, Wang Y, Geng M, Lin X, Tang W. Localization of Glucose Transporter 10 to Hair Cells' Cuticular Plate in the Mouse Inner Ear. Biomed Res Int. 2018;2018:7817453.
17. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Nat Genet. 2003;33 Suppl (3):245–54.
18. Brenet F, Moh M, Funk P, Feierstein E, Viale AJ, Socci ND, et al. DNA methylation of the first exon is tightly linked to transcriptional silencing. PLoS One. 2011;6(1):e14524.
19. Geleoc GS, Casalotti SO, Forge A, Ashmore JF. A sugar transporter as a candidate for the outer hair cell motor. Nat Neurosci. 1999;2(8):713–9.
20. Chang A, Chen P, Guo S, Xu N, Pan W, Zhang H, et al. Specific Influences of Early Acoustic Environments on Cochlear Hair Cells in Postnatal Mice. Neural Plast. 2018;2018:5616930.
21. Jiang M, Karasawa T, Steyger PS. Aminoglycoside-Induced Cochleotoxicity: A Review. Front Cell Neurosci. 2017;11:308.
22. Chen GD, Kermany MH, D'Elia A, Ralli M, Tanaka C, Bielefeld EC, et al. Too much of a good thing: long-term treatment with salicylate strengthens outer hair cell function but impairs auditory neural activity. Hear Res. 2010;265(1–2):63–9.
23. Radziwon KE, Stolzberg DJ, Urban ME, Bowler RA, Salvi RJ. Salicylate-induced hearing loss and gap detection deficits in rats. Front Neurol. 2015;6:31.
24. Bulut E, Budak M, Ozturk L, Turkmen MT, Uzun C, Sipahi T. DNA methylation of the prestin gene and outer hair cell electromotileresponse of the cochlea in salicylate administration. Turk J Med Sci. 2017;47(5):1626–33.
25. Huang ZW, Luo Y, Wu Z, Tao Z, Jones RO, Zhao HB. Paradoxical enhancement of active cochlear mechanics in long-term administration of salicylate. J Neurophysiol. 2005;93(4):2053–61.
26. Yu N, Zhu ML, Johnson B, Liu YP, Jones RO, Zhao HB. Prestin up-regulation in chronic salicylate (aspirin) administration: an implication of functional dependence of prestin expression. Cell Mol Life Sci. 2008;65(15):2407–18.
27. Li LC, Dahiya R. MethPrimer: designing primers for methylation PCRs. Bioinformatics. 2002;18(11):1427–31.
28. Bharati J, Dangi SS, Mishra SR, Chouhan VS, Verma V, Shankar O, et al. Expression analysis of Toll like receptors and interleukins in Tharparkar cattle during acclimation to heat stress exposure. J Therm Biol. 2017;65:48–56.
29. Godfrey KM, Lillycrop KA, Burdge GC, Gluckman PD, Hanson MA. Epigenetic mechanisms and the mismatch concept of the developmental origins of health and disease. Pediatric research. 2007;61(7):5–10.
30. Ralli M, Troiani D, Podda MV, Paciello F, Eramo S, De Corso E, et al. The effect of the NMDA channel blocker memantine on salicylate-induced tinnitus in rats. Acta Otorhinolaryngologica Italica. 2014;34(3):198.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Effect of Treatment Cost and Methods on Survival in Hepatocellular Carcinoma

Hepatosellüler Karsinomda Tedavi Maliyeti ve Tedavi Yöntemlerinin Sağkalım Üzerine Etkisi

Neziha Ulusoylar Erken[1], Filiz Araz[2], Ertugrul Erken[3], Birol Ozer[2]

[1]Geriatrics Clinic, Kahramanmaras Necip Fazil City Hospital, Kahramanmaras; [2]Department of Gastroenterology, Adana Training and Research Hospital, Baskent University School of Medicine, Adana; [3]Department of Nephrology, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkiye

ABSTRACT

Aim: *Survival data for patients with hepatocellular carcinoma (HCC) is heterogeneous. We aimed to analyze the survival and cost of treatment in cirrhotic patients with HCC.*

Materials and methods: *From May 1998 to March 2015, 157 patients with HCC diagnosed and treated in a single center were assessed retrospectively. Etiology, biopsy findings, Child-Pugh-Turcotte (CPT) scores, Barcelona Clinical Liver Cancer (BCLC) stages, treatment response, cost, and prognostic factors were recorded. Deaths due to complications of cirrhosis or other diseases were excluded.*

Results: *157 patients (82.8% male) with a mean age of 62.2±11.4 years at diagnosis were included. Etiology was HBV (56%), HCV (26.1%), cryptogenic (11.5%), and others (6.4%). Median lesion diameter was 4 (0.5–28) cm. 1, 2, and ≥3 lesions were present in 46.5%, 19.1%, and 34.2% of patients, respectively. Treatments were as follows: palliative (n: 53), transarterial chemoembolization-TACE (n: 53), radiofrequency ablation-RF (n: 14), radioembolization (n: 3), alcohol (n: 5), and chemotherapy (n: 14). Resection (n: 9) and transplantation (n: 6) were amenable in few patients. Before treatment, 114 (72.6%) patients were in the CPT A/B group, but 93 (59.3%) of all patients were initially staged as BCLC-C/D. Overall survival was 11.6±0.9 months, with 32% probability of surviving one year. Kaplan-Meier analysis revealed that pre-treatment CPT score, BCLC stage, TACE, and resection significantly affect survival. Cox regression defined BCLC stage (stage B: HR=9.58, 95% CI=1.03–88.98, p=0.047; stage C: HR=13.41, 95% CI=1.37–130.85, p=0.026, stage D: HR=24.72, 95% CI=2.33–262.46, p=0.008) and TACE (HR=2.36, 95% CI=1.18–4.71, p=0.015) as independent predictors of survival.*

Conclusion: *Treatment modalities were not significantly different in terms of cost (p=0, 656). Hepatocellular carcinoma was usually diagnosed late, and treatment modalities were similar in cost. Barcelona clinical liver cancer stage and TACE were predictive of survival.*

Keywords: *hepatocellular carcinoma; cirrhosis; treatment methods; survival; cost-effectiveness*

ÖZET

Amaç: *Hepatosellüler karsinom (HSK) tanısı alan hastaların sağkalım verileri farklılık göstermektedir. Çalışmamızın amacı, HSK tanısı alan sirotik hastaların tedavi ile ilişkili olarak maliyet ve sağkalım verilerini incelemektir.*

Materyal ve metot: *Mayıs 1998 ve Mart 2015 tarihleri arasında tek merkezde tedavi gören, 157 hastanın bilgileri tarandı. Etiyoloji, biyopsi sonucu, Child-Pugh-Turcotte (CPT) skoru, Barcelona Clinic Liver Cancer (BCLC) evrelemesi, tedavi cevabı, maliyet ve prognostik faktörleri kaydedildi. Siroz komplikasyonları ve diğer hastalalıklara bağlı vefat edenler çalışmadan çıkarıldı.*

Bulgular: *157 hastanın (%82,8 erkek) tanı anındaki ortalama yaşı 62,2±1,4 yıl idi. Etiyolojide HBV (%56), HCV (%26,1), kriptojenik (%11,7) ve diğer patolojiler (%19,1) mevcuttu. Ortanca kitle boyutu 4 (0,5–28) cm idi. Kitle sayılarına göre %46,5 tek kitle, %19,1'inde iki adet kitle ve %34,2 hastada ise ≥3 kitle saptandı. Uygulanan tedaviler, palyatif (n: 53), transarteriyel kemoembolizasyon-TAKE (n: 53), radyofrekans ablasyon-RF (n: 14), radyoembolizasyon (n: 3), alkol (n: 5) ve kemoterapi (n: 14) idi. Rezeksiyon (n: 9) ve transplantasyon (n: 6) sadece birkaç hastaya uygulanmıştı. Tedavi öncesi, 114 hasta (%72,6) CPT A/B idi. Fakat başlangıçta tüm hastaların %59,3'ünde (n: 93) BCLC evrelemesi B/C idi. Ortalama sağkalım 11,6±0,9 ay ve bir senelik sağkalım olasılığı %32 olarak saptandı. Kaplan-Meier analizi ile incelendiğinde tedavi öncesi CPT skoru, BCLC evresi (evre B: HR=9,58, %95 G.A.=1,03–88,98, p=0,047; evre C: HR=13,41, %95 G.A.=1,37–130,85, p=0,026, evre D: HR=24,72, %95 G.A.=2,33–262,46, p=0,008), TAKE yapılması (HR=2,36, %95 G.A.=1,18–4,71, p=0,015) ve rezeksiyon yapılmasının sağkalımla anlamlı olarak ilişkili olduğu bulundu. Cox regresyon analizine göre BCLC evrelemesinin, sağkalım üzerinde bağımsız risk faktörü olduğu saptandı. Tedavi modaliteleri arasında maliyet açısından anlamlı fark saptanmadı. (p=0,656)*

Sonuç: *Hepatosellüler karsinom tanı anında, öncelikle rezeksiyon ve transplantasyon uygunluğu değerlendirilmeli, küçük kitlelerin varlığında ise RF düşünülmelidir. Hepatosellüler karsinom için erken dönemde uygulanan küratif tedavilerin maliyet açısından daha etkin olduğunu, BCLC evresi ve TAKE uygulamasının ise sağkalım açısından önemli olduğunu gözlemledik.*

Anahtar kelimeler: *hepatosellüler karsinom; siroz; tedavi metodları; sağkalım; maliyet*

İletişim/Contact: *Neziha Ulusoylar Erken, Kahramanmaras Necip Fazil City Hospital, Geriatrics Department, 46000 Dulkadiroglu, Kahramanmaras, Türkiye* • ***Tel:*** *0533 168 71 39* • ***E-mail:*** *nezihaulusoy@gmail.com* • ***Geliş/Received:*** *23.10.2023* • ***Kabul/Accepted:*** *18.03.2024*

ORCID: *Neziha Ulusoylar Erken: 0000-0002-4878-1569* • *Filiz Araz: 0000-0003-0780-5680* • *Ertuğrul Erken: 0000-0002-7054-1203* • *Birol Özer: 0000-0001-8154-5229*

Kafkas J Med Sci 2024; 14(1):80–86
doi: 10.5505/kjms.2024.68094

Introduction

Hepatocellular carcinoma (HCC) is a tumor originating in the liver[1]. Globally, it ranks sixth among all malignancies and fourth in cancer-related deaths[2–4]. The average survival time is 6 to 20 months. This type of carcinoma is mainly observed in males between 50 and 70[5,6]. The most prominent risk factor known in the etiology is cirrhosis[7]. While alcohol consumption is the most common cause of cirrhosis-related HCC in Europe, hepatitis B (HBV) and hepatitis C virus (HCV)-associated chronic hepatitis are the leading causes in Türkiye[8]. Türkiye is in the intermediate incidence group in terms of HCC[9]. It is also established that non-alcoholic steatohepatitis (NASH) and diabetes mellitus play a role in the development of HCC[10].

Etiologic factors, clinical status of the patient, stage of the disease, and comorbidities should be assessed in the treatment of HCC, which is usually diagnosed at an advanced stage despite known risk factors. Treatment options include surgical resection, transplantation, transarterial radioembolization (TARE), percutaneous radiofrequency ablation (RFA), transarterial chemoembolization (TACE), transarterial embolization (TAE), and sorafenib. Treatments may vary depending on how advanced the disease is at the time of diagnosis, liver reserve, and comorbidities. The present study aimed to analyze the effects of different treatment options on survival and the cost of treatment in patients who were followed and treated for HCC.

Materials and Methods

This cross-sectional retrospective study was conducted in the Gastroenterology Clinic of Başkent University Adana Dr. Turgut Noyan Training and Research Hospital. The study was approved by the Başkent University Research Board (KA14/177). Three hundred potential HCC patients with International Classification of Diseases (ICD) code C22.0 who were seen in the Training and Research Hospital between June 1998 and January 2015 were analyzed. Data on the patients were obtained from the hospital data bank. Missing information and data updates were completed in consultation with patients or their relatives. Seventy-seven patients with inconsistent/uncertain pathology findings and incorrect ICD coding were excluded.

Patient Selection

From a total of 223 patients, those with a second malignancy other than HCC, fibrolamellar variant, suspicious pathology results, other primary or secondary tumors of the liver, and those with severe immunosuppressive agents were excluded. Additionally, patients with incomplete documentation, patients without regular follow-ups, and patients who died due to cirrhosis complications after HCC diagnosis were also excluded from the study (Fig. 1). After applying exclusion criteria, 157 patients diagnosed with HCC were included in the study.

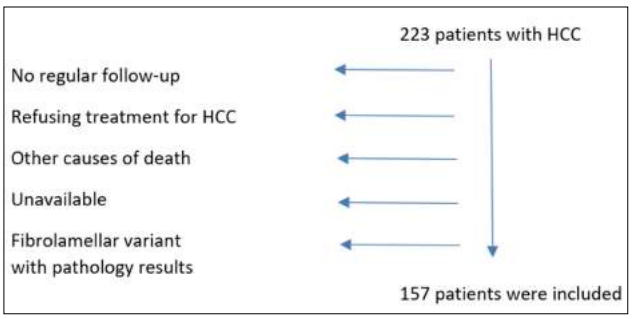

Figure 1. *Algorithm for patient selection.*

Diagnosis of Hepatocellular Carcinoma

The current guidelines of the American Association for the Study of Liver Disease (AASLD) were used to diagnose HCC[8,11,12]. The diagnosis was made by assessing serum AFP levels and radiologic imaging features (large and/or arterial hypervascularity)[11].

- For patients seen between 1998 and 2010, the AASLD 2005 guidelines (at least 1 criterion) were followed:
  - Specific radiologic sign with two different imaging modalities such as MRI, CT, or USG,
  - Alpha-fetoprotein (AFP) >200 ng/mL and specific radiologic signs by MRI or CT,
  - Pathological criterion.
- For patients seen between 2010 and 2015, the AASLD 2010 guidelines (at least 1 criterion) were utilized:
  - Specific radiologic signs by MRI or CT,
  - Pathological criterion.

Disease Burden and Prognostic Assessment

Etiology, duration of chronic liver disease, time from the diagnosis of chronic liver disease to the diagnosis of HCC, number of masses (1,2, or ≥3 (multiple)), pathology results, and treatment modalities were analyzed. Disease severity was graded based on the Child-Pugh Turcotte (CPT) and Barcelona Clinic Liver Cancer (BCLC) staging systems. The treatments (curative, palliative, or symptomatic), pre-and post-treatment CPT

and BCLC stages, AFP values, and mass sizes were recorded. All patients were subjected to survival analysis.

Cost Analysis

Treatments were divided into surgical, systemic, and local treatments. Palliative treatments were excluded from the cost analysis as they included symptomatic treatments. Total price values in terms of patient and institutional payments were calculated in Turkish Lira (TRY). The average US dollar exchange rate between 1998 and 2015 was TRY 2.03 (https: //www. tcmb. gov. tr/). Local ablative treatments were calculated proportionally to the number of applications, and systemic chemotherapy was calculated proportionally to the number of courses. Surgical procedures with a total (package) price are calculated based on this price.

Statistical Analysis

Statistical analysis was performed with the IBM Statistical Package for Social Sciences (SPSS) program version 17.0 package program. Nonparametric values were expressed as numbers and percentages, while parametric values were expressed as mean and standard deviation. Chi-square and Fisher Exact tests were employed to compare parametric data. The Mann-Whitney U test was utilized for non-normally distributed data. Survival evaluations were performed using Kaplan-Meier analysis. Cox Regression Analysis was used to analyze the factors affecting mortality based on the survival analysis results. The dependent variable in the regression analysis designed to assess risk factors on life expectancy was set at overall survival. The statistical significance level for all tests was set at p=0.05.

Results

Among the 157 patients in the study, 17.19% were women, and the mean age for all patients at diagnosis was 62.2±11.4 years. The etiology was HBV 57.3%, HCV 26.1%, NASH 3.8%, alcohol 4.4%, and cryptogenic 11.4%. The median mass size was 4.0 cm (0.5–28.0). Child-Pugh Turcotte and BCLC stages pre- and post-treatment were found to be statistically and significantly different (for both; p<0.001). Diagnostic methods, biopsy results, mass sizes, CPT – BCLC scores, and treatment modalities are summarized in Table 1.

In the pre-treatment assessment, the number of masses did not affect the CPT score at the time of diagnosis (p=0.279). Recurrence of HCC was detected in 21.7% of all patients. However, no data on the recurrence status of 39.6% of the patients could be found in the records. A total of 91.1% of the patients were found to be deceased at the time of the study, according to telephone calls and/or hospital records. The mean survival time was 11.6±0.9 months. The 12-month survival probability of patients was 32%. Factors affecting survival in HCC patients are summarized in Table 2.

Low pre-treatment CPT stage, low BCLC stage, and TACI were associated with a positive effect on survival (p<0.001 for all). Mass resection was also positively affected survival (p=0.008) (Fig. 2). Furthermore, an increase in CPT stage from A to C and BCLC stage from 0 to D were associated with a negative effect on survival. However, disease etiology, RFA, alcohol injection, or chemotherapy did not significantly affect survival (p>0.05).

Table 1. *Diagnostic methods, pathology results, mass sizes, and disease staging*

		n (%)
Diagnostic method	Radiology and AFP	34 (21.7)
	Biopsy	123 (78.3)
Pathology result	Differentiated	26 (16.6)
	Less differentiated	4 (2.5)
	Clear	3 (1.9)
	Other / mix	33 (21)
	Malignant epithelial	17 (10.8)
	Medium differentiation	6 (3.8)
	Good differentiation	17 (10.8)
	Indiscriminate[∞]	17 (10.8)
Number of audiences	1	73 (46.5)
	2	30 (19.1)
	3	16 (10.2)
	>3	38 (24.2)
Pre-treatment HSK staging	CPT stage A	62 (39.5)
	CPT stage B	52 (33.1)
	CPT stage C	43 (27.4)
	BCLC stage 0	1 (0.5)
	BCLC stage A	16 (10.2)
	BCLC stage B	47 (29.9)
	BCLC stage C	40 (25.5)
	BCLC stage D	53 (33.8)
Post-treatment HCC staging	CPT stage A	6 (3.8)
	CPT stage B	21 (13.4)
	CPT stage C	130 (82.8)
	BCLC stage 0	-
	BCLC stage A	-
	BCLC stage B	4 (2.5)
	BCLC stage C	13 (7.6)
	BCLC stage D	140 (89.8)
Treatment methods	Palliative treatment	53 (33.8)
	Trans arterial radioembolization	3 (1.9)
	Trans arterial chemoembolization	53 (33.8)
	Percutaneous radiofrequency ablation	14 (8.9)
	Alcohol injection	5 (3.2)
	Resection	9 (5.7)
	Chemotherapy	47 (29.9)
	Transplantation	6 (3.8)

[∞]There was no differentiation in the pathology report.
BCLC: Barcelona Clinic Liver Cancer; **CPT:** Child-Pugh Turcotte.

Table 2. *Survival factors and risk*

		Alive; n: 14; n (%)	Exitus; n: 143; n (%)	p
Gender (F)		4 (14.8)	23 (85.2)	0.264
Age at the time of diagnosis of HCC*		65 (16–72)	63 (27–93)	0.695
Time elapsed between the diagnosis of chronic liver disease and HCC (months)*		22 (1–141.0)	18 (0–182)	0.424
Etiology	HBV	10 (71.4)	81 (55.9)	0.080
	HCV	4 (28.6)	37(25.9)	0.760
	NASH	0 (0.0)	6 (4.2)	1.000
	Cryptogenic	1 (7.1)	17 (11.9)	1.000
	Alcohol	1 (7.1)	6 (4.2)	0.487
Mass Size (cm)		3 (1–13)	4 (0.5–28)	0.221
Number of mass	1	7 (50)	66 (46.2)	0.413
	2	4 (28.6)	26 (18.2)	
	3	2 (14.3)	14 (9.8)	
	Multiple	1 (7.1)	37 (25.9)	
Pre-treatment AFP (ng/mL) *		6.5 (1.0–1560)	318 (3–1162686)	0.0001
Post-treatment AFP (ng/mL) *		13.4 (4.0–6315)	703 (2.2–1050724)	0.056
Treatment initiation time (months)*		1.5 (0–160)	1 (0–12)	0.550
Treatments	Palliative	2(14.3)	51 (35.7)	0.142
	Radioembolization	-	3 (2.1)	1.000
	TACE	5 (35.7)	48 (33.6)	1.000
	FRG	1 (7.1)	13 (9.1)	1.000
	Alcohol injection	1 (7.1)	4 (2.8)	0.377
	Resection	1 (7.1)	8 (5.6)	0.579
	Chemotherapy	2 (14.3)	45 (31.5)	0.232
	Transplantation	2 (14.3)	4 (2.8)	0.090
Total cost (TL)*		923.1 (542.1–84086.5)	1022 (0–84000.7)	0.656
Length of stay (days)*		6.0 (2–15)	5.5 (0–26)	0.857

* average (min-max).
AFP: Alpha feto-protein; **HCC:** Hepatocellular carcinoma; **TACE:** Transarterial chemoembolization; **RF:** Radiofrequency ablation; **NASH:** Non-alcoholic steatohepatitis; **HBV:** Hepatitis B virus; **HCV:** Hepatitis C virus.

Age, baseline CPT and BCLC stages, and receipt of TACE, RFA, alcohol injection, resection, and chemotherapy were included in the regression model, analyzing the effect of treatment modalities and scoring systems on survival. Age, initial CPT stage, RFA, alcohol injection, resection, and chemotherapy alone were not found to be risk factors for survival ($p>0.05$). Pre-treatment BCLC stage and TAC were detected as independent survival risk factors. Barcelona clinic liver cancer stage 0 and CPT stage A did not affect exitus (Table 3).

The average HCC treatment for one patient was TRY 7722.50±1946.50 (approximately 3600 USD). Regardless of etiology, diagnosis mode, and size, the number of masses did not make a statistically significant difference in cost. However, it was demonstrated that as the pre-treatment CPT and BCLC stages increased, the cost spent also increased ($p=0.003$) (Table 4).

Discussion

After applying exclusion criteria, 157 HCC patients were included in this retrospective cross-sectional study. The hepatitis B virus was detected to be the primary etiologic agent, and cases were more common in the male gender. In patients diagnosed with HCC, having an early BCLC stage at the time of diagnosis and being able to perform TACE may increase survival. It was also found that patients with high CPT and BCLC stage at the time of HCC diagnosis had higher treatment costs.

HCC is closely associated with advanced liver injury and cirrhosis due to different underlying causes[13]. The most common etiologic agents are hepatitis viruses. Hepatitis B and HCV cause 60% and 33% of cases in developing countries and 23% and 20% in developed countries, respectively[12,14]. In a multicenter study involving 963 patients with chronic liver disease in Türkiye, the primary etiology for 57.6% of patients was HBV; for 16.5%, it was HCV; and for 14.2%, it was chronic alcohol use (more than ten years)[15]. The median age at diagnosis of HCC is 50–60 years in Asia and Western Europe, and it is more common in men regardless of region[16,17]. Although the mean age at diagnosis in the present study was similar to that in European countries, the interval between liver disease and tumor diagnosis was shorter. This may be due to a later detection of the disease and/or etiologic factors. It is recognized that the median survival in HCC is between 6 and 20 months[18–21]. The mean survival of the patients in this current study correlated with the literature.

When CPT and BCLC stages, which are essential in the follow-up and treatment of HCC, were evaluated,

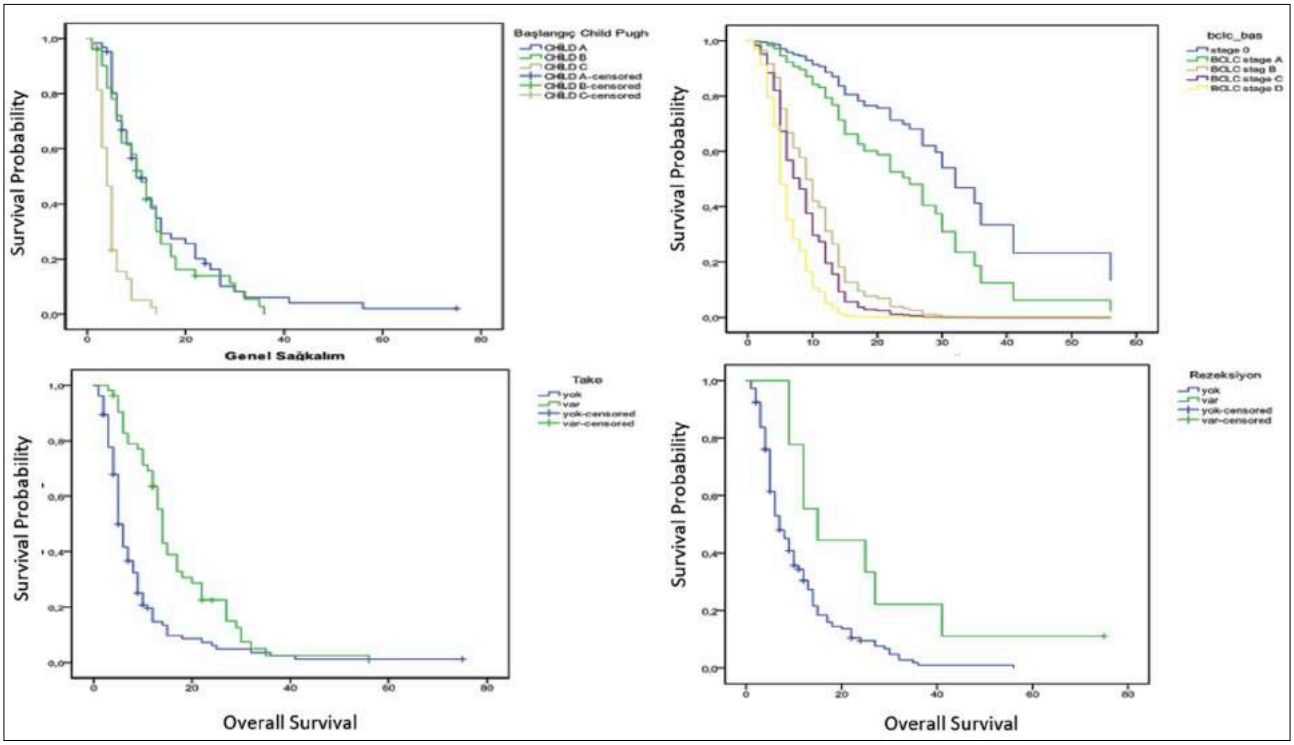

Figure 2. *Effect of scoring methods and treatments on survival.*

Table 3. *The effect of treatment methods and scoring systems on life expectancy*

	B	Standard Error	Forest	Degree of freedom	p	Hazard Risk	95% Confidence Interval
Age at the time of diagnosis of HCC	-0.01	0.009	0.33	1	0.562	0.99	0.98/1.01
CPT Stage A*	-	-	1.96	2	0.376	-	-
CPT Stage B	-0.11	0.227	0.25	1	0.616	0.89	0.57/1.39
CPT Stage C	0.35	0.359	0.93	1	0.334	1.41	0.70/2.86
TACE	0.86	0.352	5.96	1	0.015	2.36	1.18/4.71
FRG	0.32	0.340	0.86	1	0.354	1.37	0.70/2.67
Alcohol injection	0.23	0.539	0.19	1	0.663	1.26	0.44/3.64
Resection	0.54	0.468	1.32	1	0.250	1.71	0.68/4.28
Chemotherapy	0.03	0.269	0.01	1	0.903	1.03	0.61/1.75
BCLC Stage 0 *	-	-	27.69	4	0.000	-	-
BCLC Stage A	0.64	1.151	0.31	1	0.576	1.903	0.20/18.17
BCLC Stage B	2.26	1.137	3.95	1	0.047	9.58	1.03/88.98
BCLC Stage C	2.60	1.162	4.99	1	0.026	13.41	1.37/130.85
BCLC Stage D	3.21	1.205	7.08	1	0.008	24.72	2.33/262.46

*Referenced (dependent) variable.
BCLC: Barcelona Clinic Liver Cancer; **CPT:** Child-Pugh Turcotte.

it was observed that more than half of the patients in the present study were in CPT stage A. However, when tumor size, performance, and liver reserve were assessed, most of the patients were found to be in an advanced BCLC stage. The presence of HCC in the setting of advanced chronic liver disease with a high tumoral burden reduces treatment options. Tumor resection can be a curative treatment option in BCLC Stage 0 patients and BCLC Stage A patients with a single tumoral lesion, preserved liver reserve, and no portal hypertension. Liver transplantation can provide a cure for HCC patients with portal hypertension within the Milan criteria[22,23].

The present study revealed that resection and transplantation could be applied to very few patients because most had advanced liver disease and/or extensive tumors. Transarterial chemoembolization and ablative therapies have come to the forefront in patients on the liver transplant list in whom RF or surgical treatment options are not suitable as bridging therapy[24]. We observed that the TACE treatment option was

Table 4. *Cost analysis according to disease characteristics (TL)*

		n	Average	At least	At the most	p
CPT	Stage A	52	1326.2	85.8	84086.5	0.003
Before treatment	Stage B	40	923.1	103.2	84000.7	
	Stage C	10	4966.4	-	84000.7	
BCLC	Stage 0	1	542.1	542.1	542.1	0.003
Before treatment	Stage A	11	703.1	95.8	84086.5	
	Stage B	47	1002.6	542.1	9400.3	
	Stage C	35	1041.3	85.8	84000.7	
	Stage D	8	4314.3	-	84000.7	
Number of mass	1	47	1002.6	-	84000.7	0.404
	2	24	1021.9	-	84086.5	
	3	12	601.2	103.2	8628.6	
	Multiple	19	3389.8	-	10980.4	
Therapy	Resection	9	1348.4	703.1	9400.3	0.454
	Chemotherapy	47	8086.5	85.8	84086.5	0.668
	Transplantation	6	84000.7	84000.7	84086.5	<0.001
	Local ablative treatment	29	1002.6	501.3	9400.3	0.069

BCLC: Barcelona Clinic Liver Cancer; **CPT:** Child-Pugh Turcotte.

frequently used among the groups of patients included in this study, including a large number of patients for whom surgery or liver transplantation were not valid options. Several studies have compared the efficacy of TACE with resection in patients with BCLC stage B HCC. Among 171 patients with BCLC stage B and CPT stage A in a study where both methods were compared, it was revealed that the mean survival was longer in those who underwent TACE ($p<0.01$) with no significant difference in mortality rates at follow-up[25]. Another study demonstrated that the post-procedure complication rate and length of hospitalization were higher for patients with BCLC stage B HCC than those undergoing hepatic resection. According to survival rates, surgical resection was more beneficial in BCLC stage B patients with masses 1–3.

In contrast, surgical resection and TACE were similar in patients with masses >3[26]. Moreover, studies show that for cirrhotic patients with intermediate-stage HCC who can undergo mass resection, resection provides a survival advantage over TACE[27,28]. The current study revealed that TACE prolonged survival, which could be since patients at all stages were included. It can be concluded that success rates may be high at the research hospital because the TACE treatment has been used for many patients over a significant period, creating experienced treatment practitioners. RF, another ablative method and one of the curative treatments, was less preferred because most patients within the current study were in an advanced BCLC stage at the time of diagnosis. The high frequency of palliative treatment is also due to the advanced BCLC stage.

Tumor size, microvascular invasion, multifocality, and poor differentiation are key to detecting disease recurrence. In particular, poor differentiation, micro and/or macrovascular invasion, and the presence of satellitic nodules increase the recurrence rate of HCC up to 70% at 5 years[29,30]. The present research found a high recurrence rate due to the large tumor diameter at the time of diagnosis, the high number of masses, and the frequent occurrence of poor differentiation. Inadequate liver reserve at the time of diagnosis, and therefore inability to utilize curative treatments, and the growth of micronodules also increase the frequency of recurrence.

The serum AFP level in HCC patients is generally thought to be proportional to the growth activity of the tumor[18]. Therefore, a return to elevated AFP levels after treatment is interpreted as tumor growth and can be used as a survival predictor. In a study of 1579 patients with HCC, the association of AFP alone with survival was found to have a sensitivity of 52.9% and specificity of 93.3%[19]. In parallel with the literature, it was observed that in this current study, survival was low in patients with high AFP levels, which included most patients with advanced HCC. A high pre-treatment AFP value may indicate increased mortality. Another reason for the high mortality rates may be that the majority of patients were in advanced BCLC stages. However, most patients were initially diagnosed as CPT stage A. Hepatocellular carcinoma is a malignancy that often develops in the setting of chronic liver injury, and cirrhosis has a high biological variability. Its diagnosis may be delayed even during follow-up.

Considering the treatment methods selected by assessing various factors such as the number of tumoral

masses, liver reserve, stage of the disease, and supportive interventions, it is seen that HCC treatment can lead to significant health expenditures. The application of curative treatments is practical regarding both prognosis and cost[20,21,31]. This research determined that liver transplantation was more cost-effective than other treatment options. This research also demonstrated that high CPT and BCLC stages may increase healthcare expenditures. The belief is that financial spending may be higher than the general average because the patient profile had advanced stage HCC, and local ablative treatments were preferred as first-line treatment.

Conclusion

For HCC patients who are mostly diagnosed at advanced stages, with low initial BCLC stages, the possibility of curative treatment and the application of TACE as a treatment option seems to increase survival and reduce health expenditures.

References

1. Akyıldız, Ümit Yalçın KS. Hepatosellüler Karsinom Tedavisi. Güncel Gastroenteroloji 2010:184–189.
2. Bhosale P, Szklaruk J, Silverman PM. Current staging of hepatocellular carcinoma: imaging implications. Cancer Imaging. 2006;6(1):83–94.
3. Llovet JM, Villanueva A, Marrero JA, Schwartz M, Meyer T, Galle PR, et al. Trial Design and Endpoints in Hepatocellular Carcinoma: AASLD Consensus Conference. Hepatology. 2021;73 Suppl 1:158–191.
4. Kanwal F, Singal AG. Surveillance for Hepatocellular Carcinoma: Current Best Practice and Future Direction. Gastroenterology. 2019;157(1):54–64.
5. Bhosale P, Szklaruk J, Silverman PM. Current staging of hepatocellular carcinoma: imaging implications. Cancer Imaging. 2006;6(1):83–94.
6. Czauderna C, Marquardt JU, Galle PR, Wörns MA. Review of hepatocellular carcinoma: Epidemiology, etiology, and carcinogenesis. J Carcinog. 2017;16:1.
7. Collier J, Sherman M. Screening for hepatocellular carcinoma. Hepatology 27(1): p.273–278, January 1998.
8. Morgan TR, Mandayam S, Jamal MM. Alcohol and hepatocellular carcinoma. Gastroenterology. 2004;127(5 Suppl 1):S87–S96.
9. Arhan M, Akdo M, Yal M, Ka S, Tun B. Tek merkeze ait hepatosellüler karsinom veriler i;retrospektif çalışma. 2009;8(1):18–23.
10. Gilsanz Garciá V. Carcinome hépatocellulaire [Hepatocellular carcinoma]. Bull Acad Natl Med. 1989;173(3):263–282.
11. Bruix J, Sherman M;Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology. 2005;42(5):1208–1236.
12. Hartke J, Johnson M, Ghabril M. The diagnosis and treatment of hepatocellular carcinoma. Semin Diagn Pathol. 2017;34(2):153–159.
13. Villanueva A. Hepatocellular Carcinoma. N Engl J Med. 2019;380(15):1450–1462.
14. Parkin DM. The global health burden of infection-associated cancers in the year 2002. Int J Cancer. 2006;118(12):3030–3044.
15. Can A, Dogan E, Bayoglu IV, Tatli AM, Besiroglu M, Kocer M, et al. Multicenter epidemiologic study on hepatocellular carcinoma in Turkey. Asian Pac J Cancer Prev. 2014;15(6):2923–2927.
16. Kew MC. Epidemiology of chronic hepatitis B virus infection, hepatocellular carcinoma, and hepatitis B virus-induced hepatocellular carcinoma. Pathol Biol (Paris) . 2010;58(4):273–277.
17. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018;391(10127):1301–1314.
18. Piñero F, Dirchwolf M, Pessôa MG. Biomarkers in Hepatocellular Carcinoma: Diagnosis, Prognosis and Treatment Response Assessment. Cells. 2020;9(6):1370.
19. Alpha-Fetoprotein Measurement Benefits Hepatocellular Carcinoma Surveillance in Patients with Cirrhosis [published correction appears in Am J Gastroenterol. 2016;111(11):1668]. Am J Gastroenterol. 2015;110(6):836–845.
20. D'Avola D, Iñarrairaegui M, Pardo F, Rotellar F, Marti P, Bilbao JI, et al. Prognosis of hepatocellular carcinoma in relation to treatment across BCLC stages. Ann Surg Oncol. 2011;18(7):1964–1971.
21. Singal AG, Lampertico P, Nahon P. Epidemiology and surveillance for hepatocellular carcinoma: New trends. J Hepatol. 2020;72(2):250–261.
22. Bruix J, Sherman M;American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53(3):1020–1022.
23. European Association for The Study of The Liver;European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma [published correction appears in J Hepatol. 2012;56(6):1430]. J Hepatol. 2012;56(4):908–943.
24. Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst. 2008;100(10):698–711.
25. Johnson PJ, Billingham LJ. Clinical trial design in hepatocellular carcinoma. Best Pract Res Clin Gastroenterol. 2005;19(1):119–127.
26. Jianyong L, Lunan Y, Wentao W, Yong Z, Bo L, Tianfu W, et al. Barcelona clinic liver cancer stage B hepatocellular carcinoma: transarterial chemoembolization or hepatic resection? Medicine (Baltimore) . 2014;93(26):e180.
27. Chen S, Jin H, Dai Z, Wei M, Xiao H, Su T, et al. Liver resection versus transarterial chemoembolization for the treatment of intermediate-stage hepatocellular carcinoma. Cancer Med. 2019;8(4):1530–1539.
28. Lin CW, Chen YS, Lo GH, Hsu YC, Hsu CC, Wu TC, et al. Comparison of overall survival on surgical resection versus transarterial chemoembolization with or without radiofrequency ablation in intermediate-stage hepatocellular carcinoma: a propensity score matching analysis. BMC Gastroenterol. 2020;20(1):99.
29. Poon RT-P, Fan ST, Lo CM, Liu CL, Wong J. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. Ann Surg. 2002;235(3):373–382.
30. Tabrizian P, Jibara G, Shrager B, Schwartz M, Roayaie S. Recurrence of hepatocellular cancer after resection: patterns, treatments, and prognosis. Ann Surg. 2015;261(5):947–955.
31. Parikh ND, Singal AG, Hutton DW, Tapper EB. Cost-Effectiveness of Hepatocellular Carcinoma Surveillance: An Assessment of Benefits and Harms. Am J Gastroenterol. 2020;115(10):1642–1649.

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Comparison of Corneal Endothelial Parameters and Intraocular Pressure Alterations After Uneventful Cataract Surgery with 1.8% and 3% Sodium Hyaluronate

%1.8 ve %3 Sodyum Hiyalüronat ile Komplikasyonsuz Katarakt Cerrahisi Sonrası Kornea Endotel Parametreleri ve Göz İçi Basıncı Değişikliklerinin Karşılaştırılması

Emre Aydin[1], Hasan Akgoz[2], Mehmet Gokhan Aslan[3]

[1]Department of Ophthalmology, Faculty of Medicine, Samsun University, Samsun; [2]Department of Ophthalmology, Erzurum City Hospital, Erzurum; [3]Department of Ophthalmology, Faculty of Medicine, Recep Tayyip Erdogan University, Rize, Türkiye

ABSTRACT

Aim: *To assess the effectiveness and safety of two recently developed sodium hyaluronate (Na-Hy) items, differentiated by concentrations of 1.8% and 3%.*

Material and Method: *Fifty-nine uneventful phacoemulsification cataract surgeries were retrospectively evaluated. Patients were separated into two groups according to the ocular viscoelastic device (OVD) used in the capsulorhexis and phacoemulsification steps of the surgery. There were 30 patients in the 3% Na-Hy group and 29 patients in the 1.8% Na-Hy group. Patients were evaluated regarding endothelial changes by specular microscopy and postoperative intraocular pressure (IOP) alterations. Patients with systemic diseases, intraoperative complications, or mature cataracts were excluded.*

Results: *The two groups had no significant difference in demographic characteristics. Mean phaco time was 10.8±3.58 seconds in the 3% Na-Hy group and 10.55±3.85 seconds in the 1.8% Na-Hy group. The preoperative, postoperative 1st, and 3rd months endothelial cell density (ECD) measurements were 2525.8±219.7, 2304.7±197.6 and 2230.6±208.8 cells/mm^2 in the 3% Na-Hy group, and 2549.7±222.4, 2256.6±198.4 and 2166.3±201.5 cells/mm^2 in the 1.8% Na-Hy group, respectively. The preoperative, postoperative 1st day and 1st week IOP measurements were 17.1±2.56, 20.5±3.82 and 15.76±2.19 in 3% Na-Hy group and 15.96±2.56, 18.1±3.35 and 14.93±2.15 in 1.8% Na-Hy group, respectively. The reduction in endothelial cell density was notably greater in the group treated with 1.8% Na-Hy. At the same time, no significant differences were observed among the groups regarding changes in postoperative intraocular pressure (IOP).*

Conclusion: *Both Na-Hy products seem safe and effective for routine cataract cases. The 3% Na-Hy showed a better performance for corneal endothelium protection while causing minimal IOP elevation.*

Key words: *Hyotek; ocular viscoelastic device; phacoemulsification; sodium-hyaluronate*

ÖZET

Amaç: *Yeni geliştirilen, %1,8 ve %3 konsantrasyonlara farklılaştırılmış iki sodyum hiyalüronat (Na-Hy) ürününün etkinliğini ve güvenliğini değerlendirmek.*

Materyal ve Metot: *Elli dokuz komplikasyonsuz fakoemülsifikasyon katarakt ameliyatı retrospektif olarak değerlendirildi. Hastalar ameliyatın kapsüloreksis ve fakoemülsifikasyon aşamalarında kullanılan oküler viskoelastik maddeye (OVD) göre iki gruba ayrıldı. %3 Na-Hy grubunda 30, %1,8 Na-Hy grubunda ise 29 hasta vardı. Hastalar speküler mikroskopi ile endotel değişiklikleri ve ameliyat sonrası göz içi basıncı (GİB) değişiklikleri açısından değerlendirildi. Sistemik hastalıkları, intraoperatif komplikasyonları veya matür kataraktı olan hastalar çalışma dışı bırakıldı.*

Bulgular: *İki grup arasında demografik özellikler açısından anlamlı bir fark yoktu. Ortalama fako süresi %3 Na-Hy grubunda 10,8±3,58 saniye, %1,8 Na-Hy grubunda ise 10,55±3,85 saniye idi. Preoperatif, postoperatif 1. ve 3. ay endotel hücre yoğunluğu ölçümleri sırasıyla %3 Na-Hy grubunda 2525,8±219,7, 2304,7±197,6 ve 2230,6±208,8 hücre/ mm2 idi ve 1,8 Na-Hy grubunda ise 2549,7±222,4, 2256,6±198,4 ve 2166,3±201,5 hücre/ mm2 idi. Ameliyat öncesi, ameliyat sonrası 1. gün ve 1. hafta GİB ölçümleri sırasıyla %3 Na-Hy grubunda 17,1±2,56, 20,5±3,82 ve 15,76±2,19, %1,8 Na-Hy grubunda ise 15,96±2,56, 18,1±3,35 ve 14,93±2,15 idi. Endotel hücre yoğunluğundaki azalma, %1,8 Na-Hy ile tedavi edilen grupta belirgin şekilde daha fazlaydı, ancak postoperatif göz içi basıncındaki (GİB) değişiklikler açısından gruplar arasında anlamlı bir fark gözlenmedi.*

Sonuç: *Her iki Na-Hy ürünü de rutin katarakt vakalarında güvenli ve etkili görünmektedir. %3 Na-Hy, minimal GİB yükselmesine neden olurken kornea endotelini koruma konusunda daha iyi bir performans gösterdi.*

Anahtar kelimeler: *Hyotek; oküler viskoelastik madde; fakoemülsifikasyon; sodyum-hyalüronat*

İletişim/Contact: *Hasan Akgoz, Erzurum City Hospital, Erzurum, Türkiye* • ***Tel:*** *0506 672 96 35* • ***E-mail:*** *dr.hasanakgoz@gmail.com* • ***Geliş/Received:*** *23.11.2023* • ***Kabul/Accepted:*** *22.01.2024*

ORCID: *Emre Aydın: 0000-0002-1895-8538* • *Hasan Akgöz: 0000-0003-1115-8359* • *Mehmet Gökhan Aslan: 0000-0002-3250-1606*

Introduction

Cataract surgery is one of the most performed surgical interventions in the modern world. Advances in phacoemulsification energy delivery technologies and disposable products in the last three decades have provided excellent surgical results. However, new research is still on track to solve the issues for challenging eyes[1].

The loss of endothelial cells during cataract surgery leads to prolonged corneal edema and, in severe cases, may cause corneal decompensation and decreased final visual acuity[2]. Since lens removal surgery has gained a refractive surgical identity, the protection of corneal endothelium has become even more important[3]. Ocular viscoelastic devices (OVDs) are widely used to facilitate surgical procedures and reduce the risk of secondary damage to delicate intraocular tissues. They maintain anterior chamber space and stability to prevent capsular rupture and provide clarity to avoid complications[4]. These properties vary with the physical, chemical, and rheological properties of OVDs[5]. However, a longer retention time is a significant drawback of OVDs for cataract surgery. That may cause IOP elevations within the postoperative 24 hours, which may negatively impact glaucoma patients[6,7].

The OVDs are available in different concentrations and materials for particular needs. The Na-Hyaluronate (Na-Hy) is cohesive in lower concentrations but becomes more dispersive as the concentration increases. Kretz et al. reported that 3% Na-Hy covered a significantly higher rate of endothelium than 1.4% Na-Hy in porcine eyes[8]. However, Holzer et al. detected higher IOP peaks at the postoperative 4th hour with higher concentrations of OVDs[9]. Even though the OVDs are classified by their Na-Hy percentage, numerous other parameters, such as viscosity, density, and molecular weight, define their properties. Hyotek (Teknomek, Istanbul, Türkiye) is a new OVD brand available in several concentrations of Na-Hy at the same molecular weight. Therefore, they provide optimum solutions for any challenging condition in cataract surgery.

This study evaluated the corneal parameters and early postoperative IOP alterations after cataract surgery with Hyotek 3% and 1.8% Na-Hyaluronate OVDs utilized in capsulorhexis and phacoemulsification stages. Hence, the aim was to evaluate their safety and efficiency.

Materials and Methods

Ethical Approval

Before beginning the research, the Institutional Ethics Committee (E-40465587-050.01.04-131) approved it, and all researchers agreed to follow the principles of the Helsinki Declaration. The study was explained to the patients verbally, and a signed agreement was obtained from all participants.

Subject Recruitment

This retrospective observational study included 59 cataract patients aged between 50 and 80 who underwent uncomplicated surgery by the same surgeon with an Oertli Faros phacoemulsification device in a tertiary eye clinic between October 2020 and March 2021. The patients were randomly assigned into two groups: the study group with 3% Na-Hyaluronate (Hyotek, Teknomek, Istanbul, Türkiye) during the capsulorhexis and phacoemulsification stages of the surgery, and the control group with 1.8% Na-Hyaluronate (Hyotek, Teknomek, Istanbul, Türkiye) in the same stages. The technical specifications of both OVDs are shown in Table 1. The 1.4% Na-Hy injected foldable intraocular lens in all groups.

The corrected distance visual acuity (CDVA), anterior segment biomicroscopy, and corneal endothelial parameters were recorded preoperatively and 1 and 3 months after surgery. The IOP measurements were also recorded one day after the procedure. Endothelial cell density (ECD), central corneal thickness (CCT), average cell area (AVG), and cell volume (CV) were measured by noncontact specular microscopy (Tomey EM-4000, Nagoya, Japan) at each visit[10].

The corneal edema was evaluated on 1st postoperative day with the biomicroscope. It was noted as four

Table 1. *Technical specifications of the 1.8% and 3% Na-hyaluronate (Hyotek) OVDs*

Sodium Hyaluronate	Hyotek 1.8%	Hyotek 3 %
Molecular Weight	2.3-3.2 MDa	2.3-3.2 MDa
pH*	6.8-7.6	6.8-7.6
Density*	0.998-1.008 g/ml	1.001-1.020 g/ml
Viscosity*	150,000-300,000mPa.s	400,000-900,000mPa.s
Tolerance*	NA	+70,000 mPa.s
Osmolality*	200-400mOsm/kg	200-400mOsm/kg
Endotoxicity*	<0.2EU/ml	<0.2EU/ml
Refractive Index*	1.337-1.338	1.337-1.338

*After sterilization
MDa: Megadaltons; **g:** Gram; **ml:** Milliliter; **mPa.s:** Milli pascal second; **mOsm:** Milliosmole; **kg:** Kilogram; **EU:** Endotoxin units.

grades: Grade 0 (no corneal haze), Grade 1 (iris details visible), Grade 2 (pupil margin visible but iris details not visible), Grade 3 (pupil margin not visible), and Grade 4 (cornea opaque)[11].

Patients with a history of autoimmune disorder (e.g., rheumatoid arthritis, inflammatory bowel disease), corneal disorder, mature and/or Morgagnian cataract, and ocular trauma/surgery were excluded. Besides, complicated surgeries such as posterior capsule rupture, vitreous loss, postoperative inflammatory pupillary membrane, cystoid macular edema, drug allergy and/or toxicity, and patients with any missing data were also excluded.

Surgical Procedure

Local anesthesia was applied with a peribulbar injection of 4 mL 2% lidocaine. The conjunctiva was washed with 5% povidone-iodine for 3 minutes after sterile draping. Two side port incisions were created with a 19G MVR blade. Trypan blue was used to improve the visibility of the capsule. After filling the anterior chamber with 3% (Group 1) and 1.8% (Group 2) sodium hyaluronate (Hyotek, Teknomek, Istanbul, Türkiye) viscoelastic, a self-closing transparent corneal incision was created using a 2.2 mm corneal knife. 5–5.5 mm continuous circular capsulorhexis, hydro dissection, and hydro delineation were performed. In all cases, the cataractous lens was removed with the Oertli Faros phacoemulsification device using the quick chop technique with the same parameters. The cortex remnants were removed with bimanual irrigation/aspiration (I/A). The capsular bag was filled with 1.4% Na-Hy (Hyotek, Teknomek, Istanbul, Türkiye). A foldable hydrophobic intraocular lens was placed inside the capsular bag. The OVD was removed with bimanual I/A, and After administering moxifloxacin hydrochloride 0.5% (Vigamox, Alcon Labs, Fort Worth, TX) to the anterior chamber, corneal incisions were hydrated. All patients were started on antibiotics and steroid drops five times a day in the postoperative period and were given tapering doses for one month.

Statistical Analysis

Statistical analysis was conducted using IBM Statistical Package for Social Sciences (SPSS) program version 23.0 for Windows (IBM, Inc., Chicago, IL). The distribution of variables was examined through analytical methods. Descriptive statistics for normally distributed variables were presented as mean ± standard deviation. Categorical variables were analyzed using the chi-square test. Repeated-measures ANOVA was employed to compare normal values at different time points, with Bonferroni correction applied for multiple comparisons. Group differences for normally distributed variables were assessed using the independent samples t-test. All analyses were conducted with a 95% confidence interval. Statistical significance was set at $P < 0.05$.

Results

The mean age of the 59 patients included in this study was 70.23±7.10. Thirty patients were included in the 3% Na-Hy group and 29 in the 1.8% Na-Hy group. No notable distinctions were observed among the groups concerning age, gender, laterality, and phaco time. The demographic distribution of the patients is shown in Table 2.

There was no significant difference between the patients' baseline visual acuity, intraocular pressure, and corneal parameters ($p>0.05$). There were five patients with weak pupil dilatation in both groups. (16.7% and 17.2%, $p=0.953$). Significant alterations were detected in visual acuity, ECD, AVG, and CCT values in both groups at 1st and 3rd months compared to baseline (Table 3). However, CCT alterations

Table 2. *Demographic data of the patients*

	3% Na-Hyaluronate Group			1.8% Na-Hyaluronate Group			
	Mean	**SD**		**Mean**	**SD**		**p**
Age (years)	69.80	8.16		70.68	5.92		0.635[a]
Phaco Time (second)	10.80	3.58		10.55	3.85		0.799[a]
	N	Right	Left	N	Right	Left	p
Male	15	8	7	12	7	5	0.506[b]
Female	15	9	6	17	10	7	0.604[b]
Total	30	17	13	29	17	12	0.879[b]

Data are presented as mean ± standard deviation (SD).
[a]Independent sample test; [b]Chi-square test.

Table 3. *Alterations of the visual and corneal parameters in time*

	3% Na-Hyaluronate Group				1.8% Na-Hyaluronate Group			
	Pre-op	**1st month**	**3rd Month**	**p**	**Pre-op**	**1st month**	**3rd month**	**p**
CDVA (Snellen)	0.15±0.11	0.89±0.12	0.93±0.09	<0.001	0.14±0.10	0.91±0.09	0.94±0.07	<0.001
ECD (cell/mm²)	2525.8±219.7	2304.7±197.6	2230.6±208.6	<0.001	2549.7±222.4	2256.6±198.4	2166.3±201.5	<0.001
AVG	414.3±37.0	432.6±35.8	434.9±36.2	<0.001	396.8±34.1	415.3±35.1	420.7±35.6	<0.001
CV	37.0±4.2	41.5±4.4	41.8±4.8	<0.001	36.9±5.0	42.0±4.5	43.2±4.3	<0.001
CCT (µm)	533.6±39.4	558.8±40.0	548.4±38.3	<0.001	527.5±31.2	552.1±32.6	543.2±32.0	<0.001

Data are presented as mean ± standard deviation.
CDVA: Corrected distance visual acuity; **ECD:** Endothelial cell density; **AVG:** Avarage; **CV:** Cell volume; **CCT:** Central corneal thickness; **µm:** Micrometer; **mm²:** Square millimeter.
Independent Samples t-test.

Table 4. *Comparison of the alterations of both groups*

	Δ (1st month-Preop)			Δ (3rd month-Preop)			Δ (3rd month-1sth month)		
	3% Na-Hyaluronate	**1.8% Na-Hyaluronate**	**p**	**3% Na-Hyaluronate**	**1.8% Na-Hyaluronate**	**p**	**3% Na-Hyaluronate**	**1.8% Na-Hyaluronate**	**p**
CDVA (Snellen)	0.73±0.11	0.77±0.12	0.271	0.77±0.11	0.80±0.11	0.412	0.04±0.09	0.03±0.06	0.680
ECD (cell/mm²)	-224.4±56.3	-293.1±83.8	<0.001	-298.2±87.5	-383.4±105.9	<0.001	-74.0±64.6	-90.2±68.4	0.434
AVG	18.22±6.25	18.48±8.31	0.897	20.53±13.21	23.93±8.99	0.255	2.30±9.69	5.44±4.04	0.111
CV	4.50±0.97	5.06±1.30	0.062	4.86±1.56	6.31±1.79	0.002	0.36±1.27	1.24±1.02	0.005
CCT (µm)	25.13±6.65	24.58±7.26	0.764	14.76±5.70	15.68±7.15	0.585	-10.36±6.35	-8.89±7.02	0.403

Data are presented as mean ± standard deviation.
CDVA: Corrected distance visual acuity, **ECD:** Endothelial cell density, **AVG:** Avarage, **CV:** Cell volume, **CCT:** Central corneal thickness, **µm:** Micrometer, **mm²:** Square millimeter, **Δ:** Difference. Independent samples t-testp<0.05 significant values were shown in bold.

were insignificant in both groups in the 3rd month compared to preoperative measurements. (p=0.413, p=0.382, respectively)

The groups were compared in terms of ECD alterations over time, and significantly less endothelial loss was observed in the 3% Na-Hy group compared to the 1.8% Na-Hy group in both the 1st and 3rd months. Besides, the CV alteration was significantly lower in the 3% Na-Hy group between 1st-3rd months and preoperative-3rd months (Table 4).

The preoperative, postoperative 1st day, and 1st week IOP measurements were 17.1±2.56, 20.5±3.82 and 15.76±2.19 mm-Hg in 3% Na-Hy group and 15.96±2.56, 18.1±3.35 and 14.93±2.15 mm-Hg in 1.8% Na-Hy group, respectively. In both groups, the IOP value increased significantly on the 1st day. (p=0.011, p=0.043, respectively). However, there was no significant difference between the 1st week and preoperative measurements (Fig. 1).

The patients were also evaluated for corneal edema on the postoperative 1st day. No notable distinction was observed between the two groups concerning corneal edema. However, 3(+) edema was observed in 4 patients in the 1.8% Na-Hy group. In contrast, 3 (+) edema was not detected in any patient operated with 3% Na-Hy (Fig. 2).

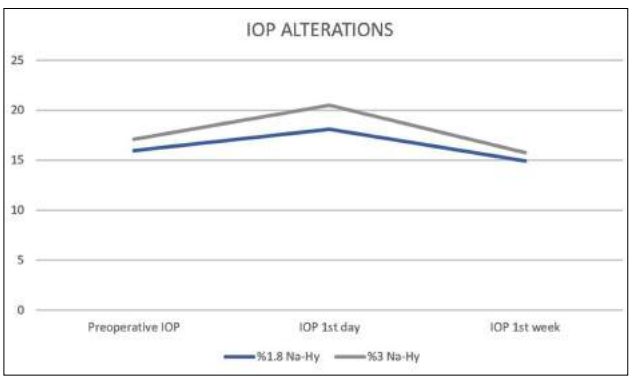

Figure 1. *Comparison of intraocular pressure change between groups.*

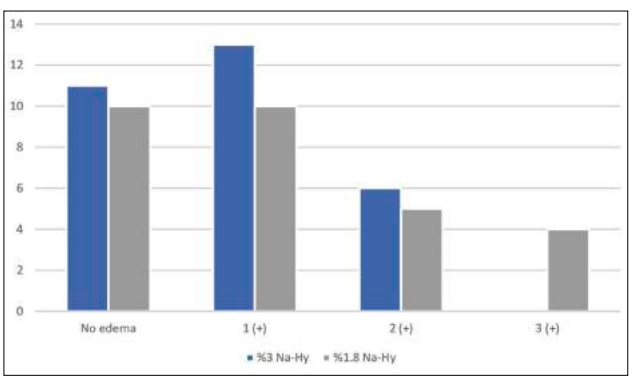

Figure 2. *Comparison of corneal edema change between groups.*

Discussion

This study evaluated the corneal endothelial and IOP alterations after uncomplicated cataract surgeries by the same surgeon (MGA) using 3% NaHy and 1.8% NaHy in capsulorhexis and phacoemulsification stages. There was no difference between the groups regarding baseline characteristics, and the same standard technique was applied. The 3% Na-Hy showed slightly better performance regarding endothelial protection, while there was no statistical difference in IOP alterations.

Cohesive viscoelastic creates a wider anterior chamber to manipulate surgical instruments and protect the corneal endothelium against iatrogenic trauma. Ben-Eliahu et al. compared various concentrations of Na-Hy. They found that all concentrations were significantly superior to irrigation to decrease endothelial oxidative stress[12]. Both 3% Na-Hy and 1.8% Na-Hy used in our study are cohesive viscoelastic. Even though the molecular weights of both concentrations were similar, the viscosity of 3% Na Hyaluronate was higher. Higher viscosity cohesive OVDs can maintain spaces and pressure the eye quite well. However, they may occasionally leave the anterior chamber too quickly in prolonged or complicated surgeries, so they afford less corneal endothelial protection in these circumstances[13]. The endothelial loss was significantly less in this study's 3% Na-Hy group. Therefore, despite the higher viscosity, 3% Na-Hy showed a sufficient performance to avoid unintentional outflow from the anterior chamber, or the higher viscosity Hyotek protects the endothelium better by causing a more expansive interior space.

Researchers have not agreed on the effects of various OVDs on endothelial cell numbers. Holzer et al. reported that Healon 5 (2%.3 Na-Hy) causes less cell loss than other Na-Hys in lower concentrations during phacoemulsification[9]. Goles et al. suggested that removing dispersive OVDs caused slightly higher postoperative endothelial cell loss than irrigation[12]. The mean endothelial cell loss was 16% with dispersive OVDs after uneventful routine phacoemulsification surgery[14]. The ECD loss in either group was assessed in this study via cell density calculation on a specular microscope. It was 11.6% in the 3% Na-Hy group and 15% in 1.8%. Na-Hy group in the 3rd postoperative month. These results suggest that high-viscosity cohesive OVDs have a similar safety index to dispersive OVDs in phacoemulsification surgery. On the other hand, this comparison would be more valuable when evaluated in complex case scenarios such as mature and Morgagnian cataracts.

The IOP alterations after cataract surgery occur on the first postoperative day and usually disappear within 3 days[15]. In particular, insufficient OVD cleaning causes a mechanical blockage at the iridocorneal angle, disrupting aqueous humor flow[16]. Apart from the classical symptoms, increased IOP may even lead to retinal artery occlusion and anterior ischemic optic neuropathy[17]. Besides, that may cause damage to the optic disc in patients with glaucoma, resulting in worsening of the visual field loss[18]. The Na-Hy-induced IOP elevation is due to its high molecular weight and viscosity[19]. While the molecular weights of the two OVDs used in our study are the same, the viscosity of the 3% Na-Hy is higher. This may explain the relatively higher increase in IOP. However, at the end of 24 hours, IOP was at normal levels in both groups, and the IOP did not exceed 30 mm-Hg in any patient. The OVDs in both concentrations were quickly removed from the anterior chamber, and the lack of significant IOP change between them can be explained by the meticulous cleaning after IOL implantation before hydrating stroma.

The migration and enlargement of central corneal endothelial cells exhibit their maximum cell density and size response, albeit delayed until three months post-surgery[20]. The Oxford Cataract Treatment and Evaluation Team recommends performing an endothelial cell count at least 90 days postoperatively, aligning with our study, to ensure stability in cell reorganization and loss[21]. Analyzing endothelial cell size and shape is a more sensitive indicator than cell count[22]. The variation coefficient (CV), a non-dimensional index ensuring a quantitative measurement of cell size variation (polymegethism), becomes crucial[23]. Matsuda et al. observed a rapid decline in central endothelial cell density and disruption of normal morphology after intracapsular cataract extraction without implant in the first month. They reported a gradual recovery of hexagonal cell frequency over 1 to 6 months postoperatively, ultimately restoring cellular morphology to normal[24]. Another study found that the size CV normalized due to the reorganization of endothelial cells one month after surgery[25]. Another study found that the size of CV normalized one month after surgery due to endothelial cell reorganization. In our study, the number of CVs in both groups changed and increased in the postoperative 1st and 3rd months compared to preoperative values. Still, this increase did not reach statistical significance. The difference in preoperative and postoperative 1st-month CV counts was similar in both groups. The increase in the number of CVs

from the 1st to the 3rd month postoperatively was significantly higher in the 1.8% Na-Hy group. That can be explained by the fact that the morphology of the cells improved quicker compared to the 3% Na-Hy group to tolerate the decrease in the ECD count since the decrease in the ECD in the postoperative 1st month was statistically higher with 1.8% Na-Hy.

Isoosmotic aqueous humor replaces OVDs after surgery, and the osmotic agent's effect rapidly diminishes. Kiss et al. showed that CCT returned to preoperative values in the postoperative 3rd month[26]. In our study, there was an increase in CCT in both groups in the postoperative 1st month and 3rd month compared to preoperative values. However, the CCT decreased in both groups in the 3rd month compared to the 1st month. A possible mechanism might be prolonged inflammation that causes corneal changes rather than the swelling of the cornea as a result of the endothelial disruption. However, long-term studies with specific measurements of each corneal layer are needed to demonstrate particular alterations. The corneal edema was significantly lower in the 3% Na-Hy group. Two mechanisms can explain that. Firstly, the low-viscosity Na-Hy may create less space during surgery, which increases the risk of instruments and/or phacoemulsification energy damaging the corneal endothelium. Besides, 3% OVDs with higher binding affinity to the corneal endothelium may cover the endothelium during phacoemulsification and irrigation/aspiration[7].

Thus, the 3% Na-Hy forms a thicker layer on the endothelium, or its binding affinity might be stronger. As the viscosity of OVDs increases, they contain a higher concentration of hyaluronan or longer chains[27]. Hence, it can be concluded that NaHy, which has a higher viscosity, can bind more to hyaluronate binding sites in the endothelium and protect the cornea better since its hyaluronan concentration is higher.

Our study had certain limitations. Firstly, the number of cases was limited, and only uneventful procedures were included. That may prevent reaching a generalized conclusion. Besides, excluding high-grade mature cataracts might prevent the evaluation of the full performance of OVDs in terms of endothelial protection. Therefore, studies assessing the performance of these OVDs in larger sample-sized groups with a wide variety of cataract populations in long-term studies are necessary. Moreover, as this study proved their safety and efficacy, these OVDs can be compared with brands containing similar molecules and concentrations.

Conclusion

As a result, these newly released OVDs containing 1.8% and 3% Na-Hy concentrations were found to be safe and effective for cataract surgery. As anticipated, the OVD containing 3% Na-Hy demonstrated greater efficacy in safeguarding endothelial function. However, no notable distinctions were detected among the groups regarding changes in IOP. Choosing 3% Na Hy in cataract patients with previous congenital and/or acquired corneal disorders may positively impact the restoration of vision after surgery.

Conflict of Interests

All authors have no conflict of interest.

Statement of Ethics

All researchers agreed to apply the tenets of the Declaration of Helsinki.

The institutional review board of X University (E-40465587-050.01.04-131) approved the study, and all participants signed a written informed consent form.

References

1. West ES, Behrens A, McDonnell PJ, Tielsch JM, Schein OD. The incidence of endophthalmitis after cataract surgery among the U. S. Medicare population increased between 1994 and 2001. Ophthalmology. 2005;112(8):1388–1394.
2. Chan E, Mahroo OAR, Spalton DJ. Complications of cataract surgery. Clin Exp Optom. 2010;93(6):379–389.
3. Grewal DS, Schultz T, Basti S, Dick HB. Femtosecond laser-assisted cataract surgery--current status and future directions. Surv Ophthalmol. 2016;61(2):103–131.
4. Linebarger EJ, Hardten DR, Shah GK, Lindstrom RL. Phacoemulsification and modern cataract surgery. Surv Ophthalmol. 1999;44(2):123–147.
5. Maár N, Graebe A, Schild G, Stur M, Amon M. Influence of viscoelastic substances used in cataract surgery on corneal metabolism and endothelial morphology: comparison of Healon and Viscoat. J Cataract Refract Surg. 2001;27(11):1756–1761.
6. Slabaugh MA, Bojikian KD, Moore DB, Chen PP. Risk factors for acute postoperative intraocular pressure elevation after phacoemulsification in glaucoma patients. J Cataract Refract Surg. 2014;40(4):538–544.
7. Malvankar-Mehta MS, Fu A, Subramanian Y, Hutnik C. Impact of Ophthalmic Viscosurgical Devices in Cataract Surgery. J Ophthalmol. 2020;2020.

8. Kretz FTA, Limberger IJ, Auffarth GU. Corneal endothelial cell coating during phacoemulsification using a new dispersive hyaluronic acid ophthalmic viscosurgical device. J Cataract Refract Surg. 2014;40(11):1879–1884.
9. Holzer MP, Tetz MR, Auffarth GU, Welt R, Völcker HE. Effect of Healon5 and 4 other viscoelastic substances on intraocular pressure and endothelium after cataract surgery. J Cataract Refract Surg. 2001;27(2):213–218.
10. Kösekahya P, Atılgan CÜ, Atılgan KG, Koç M, Tekin K, Çağlayan M, et al. Corneal Endothelial Morphology and Thickness Changes in Patients with Gout. Turkish J Ophthalmol. 2019;49(4):178–182.
11. Tandon R, Gupta N, Kalaivani M, Sharma N, Titiyal JS, Vajpayee RB. Amniotic membrane transplantation as an adjunct to medical therapy in acute ocular burns. Br J Ophthalmol. 2011;95(2):199–204.
12. Goles N, Nerancic M, Konjik S, Pajic-Eggspuehler B, Pajic B, Cvejic Z. Phacoemulsification and IOL-Implantation without Using Viscoelastics: Combined Modeling of Thermo Fluid Dynamics, Clinical Outcomes, and Endothelial Cell Density. Sensors (Basel) . 2021;21(7).
13. Poyer JF, Chan KY, Arshinoff SA. New method to measure the retention of viscoelastic agents on a rabbit corneal endothelial cell line after irrigation and aspiration. J Cataract Refract Surg. 1998;24(1):84–90.
14. Ventura AC, Wälti R, Böhnke M. Corneal thickness and endothelial density before and after cataract surgery. Br J Ophthalmol. 2001;85(1):18–20.
15. Fang EN, Kass MA. Increased intraocular pressure after cataract surgery. Semin Ophthalmol. 1994;9(4):235–242.
16. Arshinoff SA, Albiani DA, Taylor-Laporte J. Intraocular pressure after bilateral cataract surgery using Healon, Healon5, and Healon GV. J Cataract Refract Surg. 2002;28(4):617–625.
17. McCulley TJ, Miller NR. Is Cataract Surgery a Risk for Developing Nonarteritic Anterior Ischemic Optic Neuropathy? J Neuroophthalmol. 2021;41(1):119–125.
18. Llop SM, Papaliodis GN. Cataract Surgery Complications in Uveitis Patients: A Review Article. Semin Ophthalmol. 2018;33(1):64–69.
19. Miyauchi S, Iwata S. Evaluations on the usefulness of viscous agents in anterior segment surgery. II. Effect on intraocular pressure and clearance from the anterior chamber. J Ocul Pharmacol. 1989;5(3):221–232.
20. Perone JM, Boiche M, Lhuillier L, Ameloot F, Premy S, Jeancolas AL, et al. Correlation Between Postoperative Central Corneal Thickness and Endothelial Damage After Cataract Surgery by Phacoemulsification. Cornea. 2018;37(5):587–590.
21. Cheng H, Mcpherson K, Bron AJ, Kersley J, Elkington AR, Ruben M, et al. Cataract surgery: interim results and complications of a randomised controlled trial. Oxford Cataract Treatment and Evaluation Team (OCTET). Br J Ophthalmol. 1986;70(6):402.
22. Lundberg B, Jonsson M, Behndig A. Postoperative corneal swelling correlates strongly to corneal endothelial cell loss after phacoemulsification cataract surgery. Am J Ophthalmol. 2005;139(6).
23. Rao GN, Waldron WR, Aquavella J V. Morphology of graft endothelium and donor age. Br J Ophthalmol. 1980;64(7):523–527.
24. Matsuda M, Suda TI, Manabe R. Serial alterations in endothelial cell shape and pattern after intraocular surgery. Am J Ophthalmol. 1984;98(3):313–319.
25. Ravalico G, Tognetto D, Baccara F, Lovisato A. Corneal endothelial protection by different viscoelastics during phacoemulsification. J Cataract Refract Surg. 1997;23(3):433–439.
26. Kiss B, Findl O, Menapace R, Petternel V, Wirtitsch M, Lorang T, et al. Corneal endothelial cell protection with a dispersive viscoelastic material and an irrigating solution during phacoemulsification: Low-cost versus expensive combination. J Cataract Refract Surg. 2003;29(4):733–740.
27. Tomomi H, Kazuhisa S. Use of viscoelastic substance in ophthalmic surgery - focus on sodium hyaluronate. Clin Ophthalmol. 2008;2(1):21.

OLGU SUNUMU / *CASE REPORT*

Zuclopenthixol Decanoate Induced Tardive Oculogyric Crisis: A Case Report

Zuklopentiksol Dekonatın Neden Olduğu Geç Okülojirik Kriz: Olgu Sunumu

Ahmet Caliskan[1], Ibrahim Gundogmus[2]

[1]Emergency Department, Ayvalik State Hospital, Balikesir, Türkiye; [2]Psychiatry Clinic, Ankara City Hospital, Ankara, Türkiye

ABSTRACT

Zuclopenthixol is a typical antipsychotic drug used to treat schizophrenia and other psychotic disorders. Although effective and reliable, it can cause some side effects. The most common adverse effects are extrapyramidal symptoms such as akathisia, hyperkinesia, and hypokinesia. Zuclopenthixol decanoate is a long-acting form of the medication. The oculogyric crisis is the upward elevation of the gaze of both eyes within seconds to hours, resulting from the dystonic reaction of the eye muscles. It can occur as an adverse reaction to antipsychotic, antiemetic, antidepressant, antiepileptic, and antimalarial drugs. This article presents a case of tardive oculogyric crisis developed after using zuclopenthixol decanoate.

Keywords: *zuclopenthixol decanoate; tardive oculogyric crisis; schizophrenia*

ÖZET

Zuklopentiksol, şizofreni ve diğer psikotik bozuklukları tedavi etmek için kullanılan tipik bir antipsikotik ilaçtır. Etkili ve güvenilir bir ajan olmasına rağmen bazı yan etkilere neden olabilir. En yaygın yan etkileri akatizi, hiperkinezi ve hipokinezi gibi ekstrapiramidal semptomlardır. Zuklopentiksol dekanoat uzun etkili bir formdur. Oculogyric kriz, göz kaslarının distonik reaksiyonunun bir sonucu olarak her iki gözün bakışının saniyeler ila saatler içinde yukarı doğru yükselmesidir. Antipsikotik, antiemetik, antidepresan, antiepileptik ve antimalaryal ilaçların yan etkisi olarak görülebilir. Bu yazıda zuklopentiksol dekanoat kullanımı sonrası gelişen tardif okülojirik kriz olgusu sunulmaktadır.

Anahtar kelimeler: *zuklopentiksol dekonat; geç okülojirik kriz; şizofreni*

Introduction

Oculogyric crisis is a dystonic reaction characterized by the prolonged and involuntary upward deflection of the eyes[1]. This is followed by excessive and sustained upward deflection of the eyes, which is considered more characteristic. Additionally, the eyes may converge, deviating up and to the side or down. The most commonly reported associated findings are backward and lateral flexion of the neck and ocular pain[2]. Oculogyric crisis may be triggered by drugs such as antipsychotics (haloperidol, chlorpromazine, fluphenazine, olanzapine, risperidone, ziprasidone, quetiapine, clozapine, aripiprazole, and loxapine), or other drugs such as carbamazepine, chloroquine, cisplatin, diazoxide, levodopa, lithium, metoclopramide, pediapine, peclofenidone, reclospine, peclopramide; and by L acid decarboxylase deficiency, Postencephalitic Parkinson, Tourette Syndrome, Multiple Sclerosis, Neurosyphilis, head trauma, thalamic infarction, fourth ventricle lesions, cystic glioma, herpes encephalitis and kernicterus[3–6].

Zuclopenthixol is an atypical antipsychotic that is a neuroleptic of the thioxanthene group and suitable for monotherapy; it has a rapid onset of action, very few and mild adverse effects, and good tolerability[7]. Zuclopenthixol, which binds both D_1 and D_2 receptors and has a weak effect on the striatal dopamine pathway of the brain, unlike classical neuroleptics, is generally used in treatment-resistant schizophrenia cases[8]. In one study, extrapyramidal symptoms were seen in 61% of patients using zuclopenthixol at doses ranging from 50 mg to 300 mg every two weeks, and 78% required antiparkinson medication[9]. Zuclopenthixol decanoate is a long-acting form, and its side-effect profile may vary. Side effects of zuclopenthixol decanoate

İletişim/Contact: *Ahmet Caliskan, Emergency Department, Ayvalik State Hospital, Yenimahalle, Ahmet Taner Kislali Caddesi, No: 17, 10400 Ayvalik, Balikesir, Türkiye* • ***Tel:*** *0541 571 33 05* • ***E-mail:*** *drcaliskanahmet@gmail.com* • ***Geliş/Received:*** *03.12.2022* • ***Kabul/Accepted:*** *28.03.2024*

ORCID: *Ahmet Çalışkan: 0000-0002-0066-8938 • İbrahim Gündoğmuş: 0000-0002-1921-1495*

include sedation, asthenia, dystonia, akathisia, tremor, increased salivation, orthostatic dizziness, low libido, hypokinesia, rigidity, and difficulty concentrating[8,9]. However, while there are reports that oculogyric crisis may occur due to the use of zuclopenthixol decanoate, there is limited data on the occurrence of tardive oculogyric crisis[10].

In this case report, a 34-year-old male patient who experienced tardive oculogyric crisis attacks after the use of zuclopenthixol decanoate is presented.

Case

A 34-year-old male patient, single, unemployed, and a primary school graduate, living with his family, who had been diagnosed with schizophrenia, had been admitted to the psychiatry service seven times due to psychotic exacerbations. The patient was brought to the psychiatry polyclinic by his family due to the statements that people follow him, he will be harmed, his thoughts are read, and he behaves strangely. The patient was admitted to the psychiatry clinic with the diagnosis of psychotic exacerbation. Zuclopenthixol decanoate 200 mg intramuscular injection every two weeks was prescribed because of the non-compliance of the patient for the previous various antipsychotic drugs. The patient, who was in remission after eight weeks of hospitalization, was followed up by the Community Mental Health Center. It was learned that the patient had an involuntary upward deviation of the eye and ocular pain, which started four months after beginning zuclopenthixol decanoate 200 mg every two weeks.

For this reason, the patient was started on biperiden 2 mg/day. Due to the regression of the patient's complaints, it was concluded that the patient was experiencing a tardive oculogyric crisis due to zuclopenthixol decanoate. The patient's zuclopenthixol decanoate treatment was switched to aripiprazole 30 mg/day. Biperiden 2 mg/day treatment was continued for two months. Although the patient's eyes occasionally continued to turn upward, their complaints entirely resolved three months after discontinuing zuclopenthixol decanoate. The patient is still in remission with aripiprazole 30 mg/day treatment.

Discussion and Conclusion

It has been observed that zuclopenthixol, which is an atypical antipsychotic used in the treatment of psychotic disorders among psychiatric disorders, may cause oculogyric crisis, and oculogyric crisis ceases and does not recur after treatment is discontinued[11]. Praharaj et al. reported as a case report that a 21-year-old male schizophrenic patient who was treated with 200 mg depot zuclopenthixol decanoate intramuscular injection once a month experienced symptoms of tardive oculogyric crisis symptoms one and a half year after the start of the treatment and these symptoms regressed after the drug was discontinued[10].

The nigrostriatal dopaminergic pathway extending from the substantia nigra to the putamen and caudate nucleus is thought to be the underlying cause of the oculogyric crisis side effect. Antipsychotic agents cause acute dystonia by blocking dopamine D_2 receptors in the caudate, putamen, and globus pallidum[12]. It is thought that dopamine dysregulation, which causes a hypodopaminergic state, may also cause oculogyric crisis[13]. Zuclopenthixol acting by binding to D2 receptors may have caused an oculogyric crisis[8]. Since zuclopenthixol decanoate used in this case is a long-acting depot form, it may have caused delayed tardive oculogyric crisis[8]. In one study, it was shown that neuroleptic drugs that cause oculogyric crisis may also cause less frequent tardive crisis[14]. Contrary to this information, a tardive oculogyric crisis occurred in our case.

Tardive extrapyramidal symptoms are involuntary movement disorders that develop after long-term use of antipsychotic drugs. It may not improve after discontinuation of the agent used. Although it generally affects the orofacial region, it can affect the whole body. It can cause myoclonic convulsions, tics, chorea, and dystonia. Risk factors include long-term use of high-dose first-generation antipsychotics, age, female sex, and mood disorders[15]. In the case presented, there is only long-term use of antipsychotic drugs as a risk factor. In addition, a tardive oculogyric crisis that started after the long-term use of zuclopenthixol decanoate is another remarkable feature of this case report.

Drug adverse effects can be evaluated with the 10-item Adverse Drug Reaction (ADR) Probability Scale developed by Naranjo et al. According to the grading, a score of 0–13 points can be obtained, and a score of 9 and above is evaluated as "definite", between 5–8 points as "likely", between 1–4 points as "probable"and 0 points as "doubtful"[16]. When our case was evaluated according to this scale, it has got a total of 4 points due to the previous report of oculogyric crisis due to zuclopenthixol use (1 point) because the tardive oculogyric crisis occurred after zuclopenthixol decanoate was

given (2 points), because the side effect improved after zuclopenthixol decanoate was discontinued (1 point). This information suggests that the side effect may be related to zuclopenthixol decanoate.

The current report has some limitations. Zuclopenthixol decanoate plasma measurement and MRI imaging were not performed on our patient.

In conclusion, the oculogyric crisis is an essential and disturbing medical condition that negatively affects quality of life and social relations. Oculogyric crisis from zuclopenthixol is frequently seen, whereas tardive oculogyric crisis from zuclopenthixol decanoate is rarely seen. For these reasons, it is important that clinicians who will prescribe zuclopenthixol or zuclopenthixol decanoate drugs should consider this adverse effect and that clinicians evaluating patients presenting with oculogyric crisis symptoms should question the drug use in the patient's history. More controlled studies with large samples are needed to elucidate the mechanism of tardive oculogyric crisis associated with using zuclopenthixol decanoate.

References

1. Koban Y, Ekinci M, Çağatay HH, Yazar Z. Oculogyric Crisis in a Patient Taking Metoclopramide. Clin Ophthalmol. 2014;8:567–569.
2. Tatum WO, Kaplan PW, Jallon Pierre V. Nöbetler, Epilepsi A'dan Z'ye: Kısa Bir Ansiklopedi. İstanbul: Demos Medikal Yayıncılık;2009:360–1.
3. Praharaj SK, Jana AK, Sarkar Sukanto S, Vinod K. Olanzapine Induced Tardive Oculogyric Crisis. J Clin Psychopharmacol. 2009;29:604–6.
4. Virmani T, Thenganatt MA, Goldman, JS, Kubisch C, Greene PE, Alcalay RN. Oculogyric Crisis Induced by Levodopa in PLA2G6 Parkinsonism-Dystonia. Parkinsonism Relat Disord. 2014;20:245–7.
5. Tahir H, Daruwalla V. Phencyclidine Induced Oculogyric Crisis Responding Well to Conventional Treatment. Case Reports in Emergency Medicine. 2015;1–3.
6. Singh I. Prolonged Oculogyric Crisis on Addition of Nifedipine to Neuroleptic Medication Regime. Br J Psychiatry. 1987;150:127–8.
7. Amdisen A, Nielsen MS, Dencker SJ, Fensbo C, Ahlfor, UG, Gravem A, et al. Zuclopenthixol Acetate a New Drug Formulation. Acta Psych Scand. 1987;75:99–107.
8. Çetin M, Özçubukçuoğlu A, Tosuner C, Başoğlu C. Efficacy and Safety of Zuclopenthixol in Treatment-resistant Schizophrenics. BuII CIin Psychopharmacol. 1995;5:1–4.
9. Solgaard T, Kistrup K, Aaes-Jorgensen T, Gerlach J. Zuclopenthixol Decanoate in Maintenance Treatment of Schizophrenic Outpatients, Minimum Effective Dose and Corresponding Serum Levels. Pharmacopsychiatry. 1994;27:119–23.
10. Praharaj SK, Sarkhel S, Akhtar S. Stereotyped Paroxysmal Psychiatric Symptoms During Oculogyric Crisis or 'Cognitive Dystonia': A Case Report. Curr Drug Saf. 2011;6:49–50.
11. Gardner DM, Abidi S, Ursuliak Z, Morrison J, Teehan MD, Tibbo PG. Incidence of Oculogyric Crisis and Long-Term Outcomes with Second-Generation Antipsychotics in a First-Episode Psychosis Program. J Clin Psychopharmacol. 2015:35;715–8.
12. Mercan Işık C, Demirci B, Sarı SA, Uzun Çiçek A. Aripiprazole-Induced Oculogyric Crisis (Acute Dystonia) in 11-Year-Old Girl: A Case Report. Cumhuriyet Medical Journal. 2020:42;403–6.
13. Barow E, Schneider SA, Bhatia KP, Ganos C. Oculogyric Crises: Etiology, Pathophysiology and Therapeutic Approaches. Parkinsonism Relat Disord. 2017;36:3–9.
14. Haddad PM, Sharma SG. Adverse Effects of Antipsychotics: Differential Risk and Clinical Implications. CNS Drugs. 2007;21:911–36.
15. Bernardo P, Rubino A, Santoro C, Bravaccio C, Pozzi M, Pisano S. Aripiprazole-Induced Oculogyric Crisis: A Pediatric Case Series and a Brief Narrative Review. Children. 2022;9;22.
16. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts E, et al. A method for Estimating the Probability of Adverse Drug Reactions. Clin Pharm Therap. 1981;30:239–45.

OLGU SUNUMU / *CASE REPORT*

A Rare Presentation of Cystic Bronchiectasis with Acute Renal Failure and Electrolyte Imbalance

Kistik Bronşektazi ile Nadir Bir Birliktelik, Akut Renal Yetmezlik ve Elektrolit İmbalansı

Ersin Kuloglu[1], Abdulbaki Elmas[1]

[1]*Department of Internal Medicine, Faculty of Medicine, Giresun University, Giresun, Türkiye*

ABSTRACT

A 62-year-old female patient with a history of cystic bronchiectasis was brought to the emergency department with complaints of weakness, nausea, and shortness of breath. The patient was hospitalized at the internal medicine service for the accompanying acute renal failure, hypocalcemia, hypokalemia, and hypomagnesemia. The patient was started on oral active vitamin D therapy. Intravenous calcium treatment was given to the patient with a corrected calcium value of 6.4 mg/dl. In addition, intravenous potassium and intravenous magnesium replacement were performed. The patient's fluid intake and output were monitored to prevent fluid overload. The creatinine value of the patient decreased to the normal limits after five days of treatment. The patient, who had no electrolyte imbalance and whose complaints regressed, was discharged on the 8th day of hospitalization with recommendations. Clinicians should be careful about the potential risk of accompanying renal failure and electrolyte imbalance in patients with cystic bronchiectasis.

Keywords: *bronchiectasis; creatinine; acute renal failure; hypocalcemia; hypokalemia; hypomagnesemia*

ÖZET

Altmış iki yaşında kistik bronşektazi öyküsü olan kadın hasta halsizlik, bulantı ve nefes darlığı şikâyetleri ile acil servise getirildi. Hasta, eşlik eden akut böbrek yetmezliği, hipokalsemi, hipokalemi ve hipomagnezemi nedeniyle dâhiliye servisine yatırıldı. Hastaya oral aktif vitamin D tedavisi başlandı. Düzeltilmiş kalsiyum değeri 6,4 mg/dl olan hastaya intravenöz kalsiyum tedavisi başlandı. Hastaya ek olarak intravenöz potasyum ve intravenöz magnezyum replasmanı yapıldı. Hastanın volüm yüklenmesini önlemek için sıvı alımı ve idrar çıkışı izlendi. Tedaviden beş gün sonra hastanın kreatinin değeri normal sınırlara geriledi. Elektrolit imbalansı olmayan ve şikâyetleri gerileyen hasta yatışının 8. gününde önerilerle taburcu edildi. Klinisyenler, kistik bronşektazili hastalarda renal yetmezlik ve elektrolit imbalansı eşlik etme potansiyeline karşı dikkatli olmalıdır.

Anahtar kelimeler: *bronşektazi; kreatinin; akut renal yetmezlik; hipokalsemi; hipokalemi; hipomagnezemi*

Introduction

Bronchiectasis, first described by Laennec in 1819, is a long-term condition where the bronchi become permanently enlarged and thickened. This is accompanied by persistent coughing, the production of sputum, and repeated infections in the respiratory system. Bronchiectasis is divided into cylindrical, varicose, and cystic bronchiectasis according to the radiological and pathological images of the airways[1].

Case

A 62-year-old female patient with known cystic bronchiectasis, seasonal allergic rhinitis, Chronic obstructive pulmonary disease, Hypertension (HT), type 2 Diabetes Mellitus (DM), and coronary artery disease was admitted to the emergency department of our hospital on February 23rd of 2023 with complaints of weakness, nausea, shortness of breath, and weight loss. Physical examination of the patient: arterial blood pressure of 130/80 mmHg, a pulse of 102 beats per minute in sinus rhythm, and an oxygen saturation level of 97 percent. The patient was alert, oriented, and

İletişim/Contact: *Ersin Kuloglu, Giresun University Faculty of Medicine, Department of Internal Medicine, Giresun, Türkiye* • ***Tel:*** *+90 554 397 39 14* • ***E-mail:*** *ersinkuloglu.28@hotmail.com* • ***Geliş/Received:*** *26.06.2023* • ***Kabul/Accepted:*** *28.02.2024*

ORCID: *Ersin Kuloğlu: 0000-0002-8499-1926* • *Abdülbaki Elmas: 0000-0002-7524-251X*

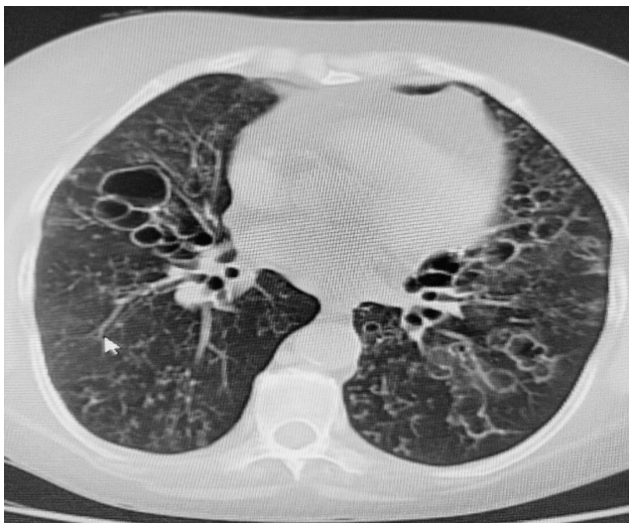

Figure 1. *Thorax tomography imaging.*

cooperative, but bilateral breath sounds were reduced during auscultation. Widespread rhonchi were heard in the bilateral lungs and rales in the basals. Although there was no tenderness, guarding, or rebounding during palpation of the abdomen, bilateral pretibial edema as grade one positive, umbilical hernia and widespread venous collaterals were detected.

Medicines used by the patient include ramipril 5 mg and hydrochlorothiazide 25 mg once a day, acetylsalicylic acid 100 mg once a day, levocetirizine and montelukast once a day, salmeterol 50 ug and fluticasone 500 ug twice a day, tiotropium 18 ug once a day, n-acetylcysteine 600 mg once a day, sitagliptin 50 mg and metformin 1000 mg twice a day, propylthiouracil 50 mg once a day. Laboratory tests in the emergency room are shown in Table 1.

Urinary system ultrasonography was performed in the emergency department to investigate the cause of acute renal failure, and no postrenal findings were observed. The cross-sectional image from the patient's thorax tomography is shown in Fig. 1. Thorax tomography was performed in the emergency department due to a complaint of shortness of breath. The report stated that the patient had calcific plaque buildup in their thoracic aorta, as well as widespread tubular cystic bronchiectasis (sequelae changes), which was more pronounced in the basal sections of both lungs; the patient also had a sliding hernia, but there was no indication of active infiltration or mass in the lung tissue (parenchyma areas); minimal fluid was present in the pleural area. Since the patient did not have typical chest pain symptoms and

Table 1. *Laboratory findings*

Parameter	Admission	Range
pH	7.35	7.35–7.45
pO_2	40	(83–108) mmHg
sO_2	%66	95–99
lactate	2.2	0.5–1.6 mmol /L
HCO_3	22.8	22–26 mmol/L
pCO_2	43	35–48 mmHg
WBC	15.520	4.000–11.000 mm^3
hemoglobin	10.2	12–16 g/dl
hematocrit	%32	36–46
MCV	78	80–96 fL
neutrophil	10.770	2.000–7.000 mm^3
lymphocyte	2760	800–4.000 mm^3
platelet	469.000	150.000–450.000 mm^3
glucose	78	74–10 mg/dl
creatinine	2.4	0.5–0.9 mg/dl
ALT	12	0–33 U/L
AST	18	0–32 U/L
total bilirubin	0.2	0–1.2 mg/dl
direct bilirubin	0.14	0–0.3 mg/dl
LDH	351	135–214 u/L
amylase	99	28–100 u/L
calcium	6.4	8.6–10.2 mmg/dl
sodium	135	136–145 mmol/L
potassium	3.2	3.5–5.1 mmol/L
CRP	93.2	0–5 mg/L
PT	9, 6	8.4–10.6 seconds
APTT	40.1	23.6–30.6 seconds
INR	1.1	0.8–1.2
albumin	4.1	3.5–5.2 gr/L
troponin T	0.03	0–0.014 microgram/L
pro BNP	705	0–125 pygogram/ml

pCO_2: Partial pressure of carbon dioxide; **MCV:** Mean corpuscular volume; **ALT:** Alanine aminotransferase; **AST:** Aspartate aminotransferase; **LDH:** Lactate dehydrogenase; **CRP:** C reactive protein; **PT:** Prothrombin time; **APTT:** Activated partial thromboplastin time; **INR:** International normalized ratio; **pro-BNP:** Pro-brain natriuretic peptides.

indicated risk factors of acute coronary syndrome, the patient's electrocardiogram (ECG) was taken to the emergency department for further examination; however, it did not reveal any indications of acute coronary syndrome. The troponin value, studied in the emergency department with 2-hour intervals, was determined as 0.03 ug/L, consistent with the previous value.

The patient was hospitalized with the diagnoses of acute renal failure, hypokalemia, hypocalcemia, hypomagnesemia, and accompanying pre-existing cystic bronchiectasis, seasonal allergic rhinitis, COPD, HT, type 2 DM, coronary artery disease, and coronary artery disease. Upon investigation of the cause of acute renal failure, it was discovered that the patient did not have a history of nonsteroidal anti-inflammatory drug use or complaints of diarrhea or vomiting; however,

the patient's daily water intake was found to be low, which could be a contributing factor to the condition. The patient was observed to be on multiple medications and had been taking ramipril 5 mg and hydrochlorothiazide 25 mg once a day for approximately one year as an antihypertensive medication.

Parathormone, phosphorus, 25-OH Vitamin D3, magnesium tests, and other routine tests were requested from the patient due to accompanying hypocalcemia. The test results were as follows; tsh: 0.5 (0.2–4.2) mu/L, ft4:1.3 (0.9–1.7) ng/dl, uric acid: 11.9 (2.4–5.7)) mg/dl, alkaline phosphatase (ALP): 69 (30–120) U/L, gamma-glutamyl transferase (GGT): 12 (5–36) U/L, magnesium: 1.0 (1.6–2, 6) mg/dl, phosphorus: 4.2 (2.5–4.5) mg/dl, parathormone: 131 (15–65) ng/L, procalcitonin: 0.12 (0–2) ug/L, 25-OH Vitamin D3:2.47 (20–50) ng/ml, iron: 53 (37–145) ug/dl, iron-binding: 223 (135–392) ug/dl, ferritin: 150 (13–150) ug/L, folate: 9.9 (3.8–20) ug/L, b12:417 (197–771) nanogram/L

Acute renal failure, severe vitamin D deficiency, hypocalcemia, hypomagnesemia, and hypocalcemia were detected in the patient. The patient's treatment with sitagliptin+metformin and ramipril+hydrochlorothiazide was discontinued. Blood pressure was monitored, and 10 mg of amlodipine was ordered daily if necessary. The patient was started on oral active vitamin D therapy. Intravenous calcium treatment was given to the patient with a corrected calcium value of 6.4 mg/dl. In addition, intravenous potassium and intravenous magnesium replacement were performed. The patient's fluid intake and output were monitored to prevent fluid overload, and the fluid intake was followed up to be 500 cc more than the fluid output. Laboratory findings after treatment are shown in Table 2. The creatinine value of the patient was within normal limits. The patient, who had no electrolyte imbalance and whose complaints regressed, was discharged on the 8th day of hospitalization with recommendations.

Table 2. *Laboratory findings after treatment*

Parameter	Level	Range
magnesium	1.9	1.6–2.6 mg/dl
glucose	84	74–10 mg/dl
creatinine	0.8	0.5–0.9 mg/dl
ALT	10	0–33 U/L
AST	14	0–32 U/L
total bilirubin	0.2	0–1.2 mg/dl
direct bilirubin	0.	0–0.3 mg/dl
LDH	208	135–214 u/L
calcium	8.5	8–6–10.2 mg/dl
sodium	135	136–145 mmol/L
potassium	4.5	3.5–5.1 mmol/L
CRP	4	0–5 mg/L

ALT: Alanine aminotransferase; **AST:** Aspartate aminotransferase; **LDH:** Lactate dehydrogenase; **CRP:** C-reactive protein.

Discussion and Conclusion

Recent scientific research in Türkiye indicates that the etiological factors that cause the development of bronchiectasis can be revealed in more than half of the patients. While some identifiable causes of bronchiectasis are localized to the lung, others are a component of systemic diseases. Pneumonia and other lower respiratory tract infections rank first among the causes of bronchiectasis[2]. Investigation of the underlying etiology is recommended in all patients with bronchiectasis. Childhood viral and bacterial respiratory tract infections are thought to play a role in developing bronchiectasis[1]. Although complications such as lung abscess, empyema, metastatic brain abscess, and amyloidosis have been reported due to bronchiectasis, these conditions are rarely observed with the use of selected antibiotics today. Patients diagnosed with concomitant cystic fibrosis during pediatric age have a short life expectancy, and around 50% of them may live beyond the age of 30. During bronchiectasis, patients commonly experience acute exacerbations of pneumonic infections, hemoptysis (coughing up blood), COPD, and cor pulmonale (enlargement and dysfunction of the right side of the heart due to lung disease)[3]. Bronchiectasis not caused by cystic fibrosis can be treated with several options, including medical treatment such as antibiotics and bronchodilators, physiotherapy, and surgical treatment[3].

According to a report on comorbid diseases in patients with bronchiectasis, at least one additional comorbid disease was observed in 44% of 138 patients followed in the departments of Chest Diseases and Thoracic Surgery at Atatürk University Training and Research Hospital. These were respectively COPD (23.1%), sinusitis (15.2%), hypertension (13.7%), peptic ulcer (10.8%), heart failure (10.1%), hepatitis (3.6%) and other (7.0%)[4].

In a multicenter study investigating the etiology in 287 amyloidosis patients in Türkiye, familial Mediterranean fever (FMF) was reported as the cause in 64%, tuberculosis in 10%, bronchiectasis, and COPD in 6%, rheumatoid arthritis in 4%, spondyloarthropathy in 3%,

chronic osteomyelitis in 2%, other causes in 4%, and unknown causes in 7%. Bronchiectasis and COPD were ranked third among the causes. Bronchiectasis can play a role in the etiology of chronic kidney failure secondary to amyloidosis[5].

Upon reviewing the literature, no direct study investigated the association between bronchiectasis and acute renal failure-electrolyte imbalance. Studies have shown that inflammatory markers are elevated in patients with concomitant bronchiectasis, especially in the geriatric population. The association between bronchiectasis and an inflammatory profile is thought to contribute to the development of acute renal failure. Electrolyte imbalance can occur in patients with diseases secondary to acute renal failure. Patients with bronchiectasis, who are treated with antihypertensive medications such as ACE inhibitors or angiotensin II receptor blockers, as well as diuretics (loop, thiazide, thiazide-like), should be monitored for electrolyte imbalance, as in our case.

This case gains importance due to being the first case reported in the literature where both electrolyte imbalance and acute kidney failure accompany cystic bronchiectasis. Although acute kidney failure is a common cause of most electrolyte imbalances (such as hyperkalemia and hyponatremia), the coexistence of hypokalemia and hypocalcemia is a rare condition. Chronic granulomatous diseases, among the causes of non-cystic bronchiectasis, are also associated with hypercalcemia. This shows us that, contrary to what we expect in our case, bronchiectasis patients may present with many electrolyte imbalances[6].

Bronchiectasis is significant in pediatric and respiratory disease practice and requires attention in internal medicine clinics and accompanying internal pathologies. Early detection and management of these accompanying internal pathologies can improve bronchiectasis patients' overall prognosis and quality of life. Further research is needed to understand better the mechanisms linking bronchiectasis and these comorbidities and develop more effective treatment strategies for this complex disease.

Financial Support and Interest Relationship

No person/organization financially supports the study, and the authors do not have any conflicts of interest.

References

1. Barker AF. Bronchiectasis. The New England journal of medicine. 2002;346(18):1383–93.
2. Pasteur MC, Bilton D, Hill AT. British Thoracic Society guideline for non-CF bronchiectasis. Thorax. 2010;65 Suppl 1:i1-i58.
3. Bülbül Y, Erçen Diken Ö, Uğur Chousein EG. [Bronchiectasis in Turkey: Under the light of national publications]. Tuberkuloz ve toraks. 2020;68(1):48–65.
4. Alpar S, Lakadamyalı H, Gürsoy G, Baştuğ T, Kurt B. 138 bronşektazili olgunun retrospektif olarak irdelenmesi. Solunum. 2002;4:396–401.
5. Tuglular S, Yalcinkaya F, Paydas S, Oner A, Utas C, Bozfakioglu S, et al. A retrospective analysis for etiology and clinical findings of 287 secondary amyloidosis cases in Turkey. 2002;17(11):2003–5.
6. Akçay Ş, Akman B, Özdemir H, Eyüboğlu FO, Karacan Ö, Özdemir N. Bronchiectasis-related amyloidosis as a cause of chronic renal failure. Ren. Fail. 2002;24(6):815–23.