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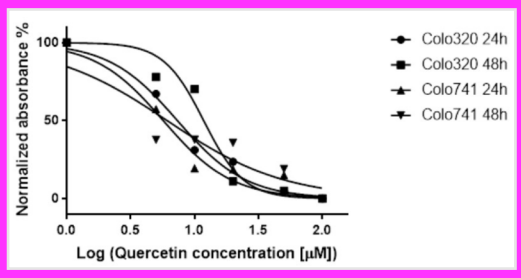

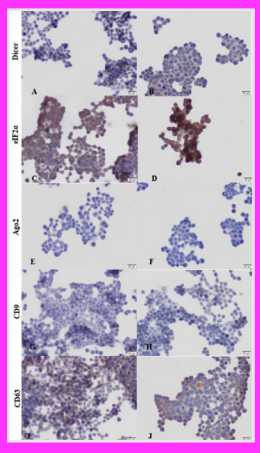

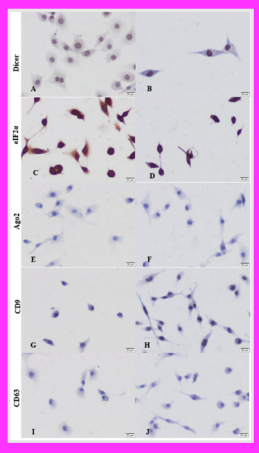

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7. References are welcomed and should not be more than 5.

8. Video and images must be cited within main text.

9. There should be no identification of patient / physician / institution / city / country in pictures and especially video images.

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Book Section: Sherry S. Detection of thrombi. In: Strauss HE, Pitt B, James AE, editors. Cardiovascular Medicine.St Louis: Mosby; 1974.p.273-85.

Books with Single Author: Cohn PF. Silent myocardial ischemia and infarction. 3rd ed. New York: Marcel Dekker; 1993.

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Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992.p.1561-5.

Scientific or Technical Report: Smith P. Golladay K. Payment for durable medical equipment billed during skilled nursing facility stays. Final report. Dallas (TX) Dept. of Health and Human Services (US). Office of Evaluation and Inspections: 1994 Oct. Report No: HHSIGOE 169200860.

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Thesis: Kaplan SI. Post-hospital home health care: the elderly access and utilization (dissertation). St. Louis (MO): Washington Univ. 1995.

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Epub ahead of print Articles: Aksu HU, Ertürk M, Gül M, Uslu N. Successful treatment of a patient with pulmonary embolism and biatrial thrombus. Anadolu Kardiyol Derg 2012 Dec 26. doi: 10.5152/akd.2013.062. [Epub ahead of print]

Manuscripts published in electronic format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) l995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/www.cdc.gov/ncidodlElD/cid.htm.

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EDITORIAL

Dear Readers;

We are together with you, our valued readers, in the last issue of 2023. It has been a year where we have experienced together the advantages and disadvantages of publishing in a multidisciplinary field. We strive to have an article from every discipline in each issue. The fact that the numbers coming from some disciplines are higher puts us in a difficult situation in this effort. For this reason, there may be some delays in the publication of some articles, I believe you will understand this. We will be with you again in the coming period with intense effort and cooperation, and we will mostly include original and experimental studies.

In this issue, we chose our cover image from Becer E et al.'s article titled "Quercetin Change the Exosome Secretion and Total miRNA Concentration in Primary (Colo320) and Metastatic (Colo741) Colon Cancer Cell Lines". The study aimed to determine the effects of quercetin, which is considered a potential anti-cancer agent in the prevention of colon cancer, on the cytotoxicity of Dicer, Ago2, eIF2α CD9 and CD63 and exosomal miRNA secretion and expression in Colo320 and Colo741 colon cancer cell lines. We included it on the cover because it was a first-step tissue culture study to produce new active ingredients in the fight against cancer, one of the diseases that caused the most deaths today.

Our featured articles are as follows:

2-How The Pandemic Has Affected Children's Weight and Height?-A Single Center Experience Nevin Cambaz Kurt, Tülin Kurtul Demirhan, Ahmet Sert, Habip Balsak, Hasan Önal; İstanbul, Ankara, Batman, Turkey

3- Chemical Composition and In Vitro Cytotoxicity of Endemic Thymus brachychilus Jalas Against Human Breast Adenocarcinoma (MCF-7, HTB-22), Human Lung Adenocarcinoma (A549, CRM-CCL-185), and Human Glioblastoma Cells (U-118 MG, HTB-15) Ebru ÖZDEMİR NATH, Mahmoud ABUDAYYAK, İlker DEMİRBOLAT, Sefa SÖNMEZ, Murat KARTAL; İstanbul, Turkey

4- Are Refugee and Native Patients' Self-Care Agencies the Same?-A Cross-sectional Study in Chronic Hemodialysis Patients in Turkey Neşe KISKAÇ, Mahruk RASHİDİ, Egemen CEBECİ, İlkay ÇOBAN, Abdüsselam ŞEKERCİ; İstanbul, Turkey

5- Heat Stress Alters Oxidative and Inflammatory Responses in Many Tissues of Male Rats Esra ŞENTÜRK, Hilal ÜSTÜNDAĞ; Ağrı, Erzincan, Turkey

It will be our pleasure to be with you in our new issues in 2024. I would like to thank the new assistant editors and section editors who joined us this year, and the newly added referees to our staff. I would like to state that their scientific contributions are very valuable to us.

Dear scientists and our valued readers, I wish all the best to see you in the new issues in the new year...

Kind regards,
Prof. Dr. Adem AKÇAKAYA
Editor in Chief

Original Article

DOI: 10.14235/bas.galenos.2023.60566
Bezmialem Science 2023;11(4):335-342

Quercetin Change the Exosome Secretion and Total miRNA Concentration in Primary (Colo320) and Metastatic (Colo741) Colon Cancer Cell Lines

Kersetin Primer (Colo320) ve Metastatik (Colo741) Kolon Kanseri Hücre Dizilerinde Eksozom Salgısını ve Total miRNA Konsantrasyonunu Değiştirir

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[4]Near East University, DESAM Research Institute, Nicosia, North Cyprus

ABSTRACT

Objective: Quercetin, which is considered a potential anti-cancer agent in the prevention of colon cancer, is one of its natural polyphenolic compounds. Extracellular vesicles, such as exosomes, secreted from cells and their components contribute to cellular behavioral characteristics by transporting proteins or miRNAs. In this study, we aimed to determine the cytotoxicity of Dicer, Ago2, eIF2α CD9 and CD63 and their effects on exosomal miRNA secretion and expression in Colo320 and Colo741 colon cancer cell lines applied quercetin.

Methods: The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) assay was used to analyze the cytotoxicity of quercetin. MTT analysis is a colorimetric analysis method applied to measure the metabolic activity of cells. The absorbance was measured at 570 nm by a spectrophotometer. Besides that, the indirect immunoperoxidase staining was used for the distribution of Dicer, Ago2, eIF2α, CD9, and CD63 in Colo320 and Colo741. Total miRNA in exosome was determined with miRCURY™ Kit.

Results: The immunoreactivities of eIF2α and CD9 significantly differed compared to the Colo741 control group after quercetin application. In addition, exosomal miRNA concentrations were higher in both quercetin applied-Colo320 and Colo741 cells.

ÖZ

Amaç: Kolon kanserinin önlenmesinde potansiyel bir anti-kanser ajan olarak kabul edilen kersetin, doğal polifenolik bileşiklerinden biridir. Hücrelerden ve bileşenlerinden salgılanan eksozom gibi hücre dışı veziküller, proteinleri veya miRNA'ları taşıma yoluyla hücresel davranış özelliklerine katkıda bulunur. Bu çalışmada, kersetin uygulanan Colo320 ve Colo741 kolon kanseri hücre dizilerinde Dicer, Ago2, eIF2α CD9 ve CD63'ün sitotoksisitesini ve eksozomal miRNA salgılanması ve ekspresyonu üzerine etkilerini belirlemeyi amaçladık.

Yöntemler: Kersetin sitotoksisitesinin analizi için MTT testi kullanıldı. Colo320 ve Colo741'de Dicer, Ago2, eIF2a, CD9 ve CD63'ün dağıtımı için dolaylı immünoperoksidaz boyaması kullanıldı. Eksozomdaki toplam miRNA, miRCURY™ Kit ile belirlendi.

Bulgular: Kersetin uygulamasından sonra eIF2a ve CD9 immünoreaktiviteleri Colo741 kontrol grubuna kıyasla önemli ölçüde farklılık gösterdi. Ayrıca eksozomal miRNA konsantrasyonları hem kersetin uygulanan Colo320 hem de Colo741 hücrelerinde daha yüksekti.

Sonuç: Kersetin uygulamasının Colo320 ve Colo741 hücrelerinde eksozomal salgılamayı tetiklediği sonucuna vardık. Bununla birlikte, primer ve metastatik kolon adenokarsinom hücrelerinde kersetin

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ABSTRACT

Conclusion: We concluded that quercetin triggered exosomal secretion in Colo320 and Colo741 cells. However, exosomal component should be evaluated in future investigations to understand the quercetin role in primary and metastatic colon adenocarcinoma cells.

Keywords: Colon cancer, exosomes, miRNA, quercetin

ÖZ

rolünü anlamak için gelecekteki araştırmalarda eksozomal bileşen değerlendirilmelidir.

Anahtar Sözcükler: Kolon kanseri, eksozomlar, miRNA, kersetin

Introduction

Colorectal cancer (CRC) is a severe gastrointestinal malignancy of which frequency is rapidly increasing worldwide (1). The risk of CRC increases with smoking, unhealthy lifestyle habits, and poor diet (2). The tumor microenvironment (TME) is critical in the survival and metastatic properties of CRC cells. TME refers to the cellular environment in which the tumor interacts, and this cellular environment includes cancer cells, immune cells, fibroblasts, cytokines, vascular tissue, extracellular matrix and proteins that contribute to tumor growth. It is emphasized that the TME is an important factor contributing to the development of resistance to cancer therapy. Cellular and non-cellular components of TME are important in contributing to CRC progression and metastasis. TME helps cancer cells to communicate with stromal cells and arranges the secretion of different proteins or exosomes which play crucial roles in the features of CRC cells (3,4). The development of new biomarkers is a vital strategy for public health to decrease the mortality of CRC effectively. Recent experimental studies have shown that exosomes may be important biomarker sources in CRC (5).

Exosomes are small membrane vesicles (50-150 nm) excreted from different cells including cancer cells. They contain protein, RNAs (microRNAs, mRNAs, long noncodingRNAs) organels etc (6,7). Also, the composition of exosomes alters according to cell type and includes specific membranous markers such as CD9, CD81, CD63 etc. (8). Many studies suggested that proteins and/or miRNAs carrying with exosomes might effectively control the tumorigenesis, surveillance and resistance of CRC (9,10). Moreover, the exosomal miRNAs can be used to recognize and track the cancer cells (11,12).

The genes encoding miRNAs are much longer than the processed mature miRNA molecule. Many miRNAs are known to reside in introns of their pre-mRNA host genes and share their regulatory elements, primary transcript, and have a similar expression profile. For the remainder of miRNA genes that are transcribed from their own promoters, few primary transcripts have been fully identified. MicroRNAs are transcribed by RNA polymerase II as large RNA precursors called pri-miRNAs and comprise of a 5' cap and poly-A tail (13). The pri-miRNAs are processed in the nucleus by the microprocessor complex, consisting of the RNase III enzyme Drosha, and the double-stranded-RNA-binding protein, Pasha/DGCR8. The resulting pre-miRNAs are approximately 70-nucleotides in length and are folded into imperfect stem-loop structures. The pre-miRNAs are then exported into the cytoplasm by the karyopherin exportin 5 (Exp5) and Ran-GTP complex. Ran (ras-related nuclear protein) is a small GTP binding protein belonging to the RAS superfamily that is essential for the translocation of RNA and proteins through the nuclear pore complex. The Ran GTPase binds Exp5 and forms a nuclear heterotrimer with pre-miRNAs. Once in the cytoplasm, the pre-miRNAs undergo an additional processing step by the RNAse III enzyme Dicer generating the miRNA, a double-stranded RNA approximately 22 nucleotides in length. Dicer also initiates the formation of the RNA-induced silencing complex (RISC) (14). RISC is responsible for the gene silencing observed due to miRNA expression and RNA interference (15-19).

Therefore, miRNAs and factors of miRNAs biosynthesis are significant post-transcriptional modulators that have vital and critical roles in both health and disease. For this reason, miRNAs and their biogenesis factors, such as Drosha, Dicer, and Ago2, are being extensively studied for the target treatment of cancers (20,21).

In treating CRC, multi-targets and various action mechanisms with decreased toxicity have improved clinical outcomes. In the last decade, use of polyphenolic compounds with chemotherapeutic drugs demonstrated their synergistic effects on cancer cells. Dietary polyphenolic compounds affect different molecular procedures by acting as chemopreventive blockers in CRC (22). One of the polyphenolic compounds, quercetin, is being investigated with relevance to its anticancer activity on CRC. Experimental studies showed that different concentration and application period for quercetin were impressive in inhibiting cancer formation and cell death, viability and mitosis (23,24). Moreover, it is thought that the anti-cancer properties of quercetin may be related to its structure and exosomal secretions including miRNAs levels in CRC (20,21).

Recent evidence indicated that the polyphenolic compound, quercetin could be potential as new therapeutic tool in cancer treatment because of its anti-oxidant, anti-inflammatory and anti-cancer effects. In contrast to that, the role of quercetin on secretion of exosome and its related components and also miRNA levelshas not been elucidated in colon cancer cells and also a comparison between primary CRC cancer cells and metastatic cells has not been performed. Additionally, dysregulation of eukaryotic translation initiation factor 2α (eIF2α) which is a

critical factor during protein synthesis is related with metabolic disorders including cancer (25). The limited experimental studies have addressed the effects of quercetin on the expression of eIF2α in CRC. In this study, we aimed to search the role of quercetin on secretion of exosome, its related components and also miRNA levels in Colo320 and Colo741 CRC cell lines.

Methods

Cell Culture

Primary (Colo320, ATCC: CCL-220.1) and metastatic (Colo741, ECACC: 93052621) CRC cell lines were cultured in RPMI 1640 (Biochrom; FG- 1215) medium containing Fetal Bovine Serum (10%, FBS, Capricorn Scientific), 1% penicillin-streptomycin [1%, (Biochrom; A- 2213)], and L- glutamine (1%, EMD Millipore; K- 0282) at a 37 ˚C and 5% CO_2 in atmosphere.

Cytotoxicity Analyze

The cell cytotoxicity of quercetin was performed with 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide assay (MTT, Fisher, 158990050). The MTT assay was performed according to the principles we reported previously (26). Colo320 and Colo741 cells were administered with different quercetin (Sigma; Q- 4951) concentrations (5, 10, 25, 50 and 100 µg/mL) for 24 h or 48 h.

Immunocytochemical (IHC) Analyses

The both types of cells were cultured in other culture medium with or without quercetin for 48 h. Dicer, eIF2c (Ago2), eIF2α, CD63, and CD9 distributions were evaluated with indirect immunoperoxidase staining protocols in Colo320 and Colo741 cells as we previously described (26). Fixation was performed with 4% paraformaldehyde on all cells from all groups for 30 min. They were washed with phosphate buffer saline (PBS) and then incubated with 3% of H_2O_2, then with blocking agent solution (ready to use, Thermo scientific, TP-125-HL). Primary antibodies against Dicer (Santa Cruz sc- 136981), eIF2α (Santa Cruz sc- 133132), Ago2 (Santa Cruz sc- 376692), CD9 (Santa Cruz sc- 13118) and CD63 (Santa Cruz sc- 5275) were added and incubated overnight at 4 °C. The cells from all groups were washed with PBS and biotinylated secondary antibody and streptavidin-peroxidase complex were added (ready to use, Thermo scientific, TP-125-HL), respectively. After washing with PBS, diaminobenzidine was added for 5 min. The counterstain was performed with Mayer's hematoxylin solution (Bio Optica; 1213). The mounting medium was applied and H-SCORE semi-quantitative grading evaluation was used for antibodies intensity (24).

miRNA Analyzes

The culture medium from all groups were collected and exosome and total miRNA levels were measured according to the manufacturer's of miRCURY™ RNA isolation kit (cat no/ ID 76743).

Data Analysis

Mean ± standard deviation was used for data expression in the assay. All data were analyzed statistically with GraphPad software. The differences were evaluated using Mann-Whitney U tests and a $p<0.05$ was considered statistically significant. All experiments were done in triplicate.

Results

After cytotoxicity analyses, 25 µg/mL of quercetin administration for 48 hours was suitable for both Colo320 and Colo741 cells (Figure 1).

The intensity of dicer was weak in Colo320 cells after quercetin administration, but, it was not significant when compared with control Colo320 cells (Figure 2A, B, Table 1). The vigorous intensity of eIF2α in both control (Figure 2C) and quercetin administrated (Figure 2D) Colo320 cells was observed; however, this immunoreactivity was not statistically significant (Table 1). Similar and weak Ago2 and CD9 immunoreactivities were detected in both groups of Colo320 cells (Figure 2E-2H, Table 1). The immunoreactivity of CD63 was moderate and not significant in both groups of Colo320 cells (Figure 2I, 2J, Table 1).

In Colo741, metastatic colon adenocarcinoma cells, Dicer immunoreactivity was strong and not significant in both groups (Figure 3A, 3B, Table 1). Decreased and statistically significant immunoreactivity of eIF2α after quercetin application was detected in Colo741 cells (Figure 3C, 3D, Table 1). The intensity of Ago2 was weak and similar in both groups of Colo741 cells (Figure 3E, Figure 3F). The CD9 immunoreactivity was vigorous after quercetin application on Colo741 cells (Figure 3H), and it was statistically significant when compared with control Colo741 cells (Figure 3G, Table 1). Weak and similar CD63 immunoreactivity was detected in both groups of Colo741 cells (Figure 3I, and Figure 3J).

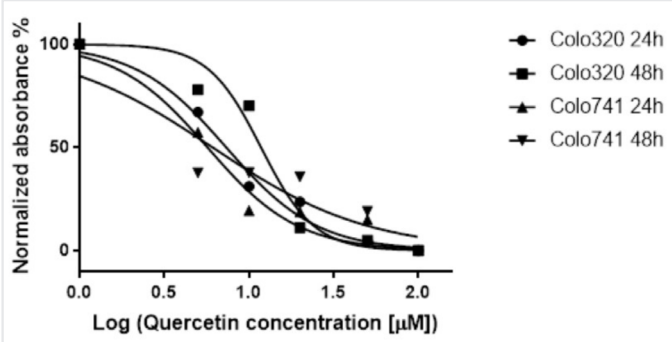

Figure 1. MTT assay results and calculated IC_{50} values for Colo320 and Colo741 cancer cells after quercetin application. Colo320 and Colo741 cells were applied at five different concentrations (5-100 µM) for 24 and 48 h. Cell viability was affected by dose and incubation time. In the experiments, 25 µg/mL of quercetin for 48 hours was used as the effective dose and incubation time

After quercetin application on both Colo320 and Colo741 cell lines, total exosomal miRNA concentrations were detected as 12.13 ng/μL and 15.15 ng/μL, respectively. Higher but not significant the total miRNA concentration was calculated in quercetin-applied both Colo320 and Colo741 colon adenocarcinoma cell lines than in control cell lines.

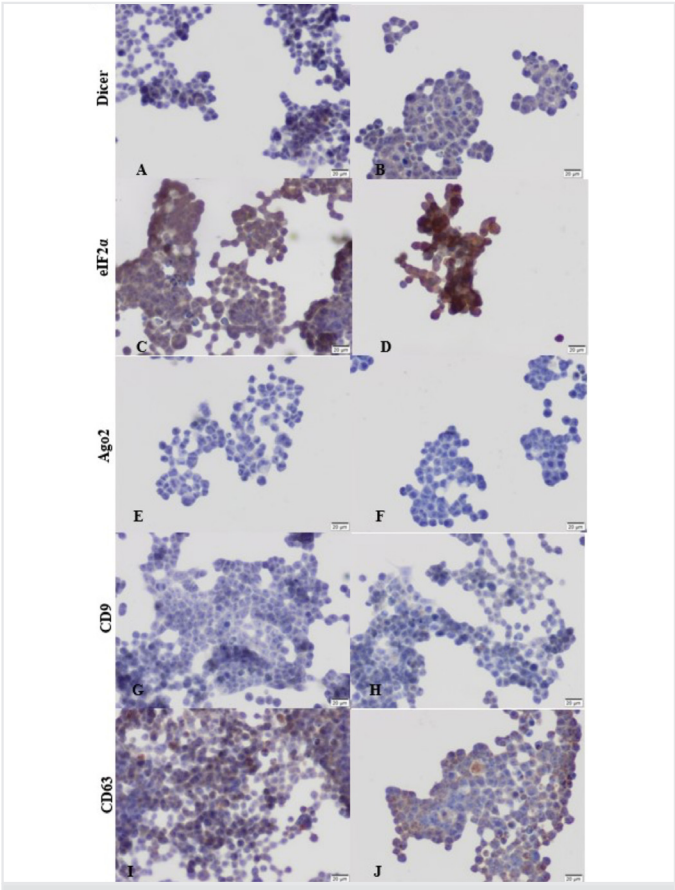

Figure 2. Dicer (A, B), eIF2α (C, D), Ago2 (E, F), CD9 (G, H), CD63 (I, J) immunoreactivity in control (A, C, E, G, I) and 25 μM quercetin-applied (B, D, F, H, J) Colo320 cells. Morphological changes were observed in the cells after quercetin application. Scale bars = 20 μm

Table 1. Evaluation of H-SCORE intensity of related antibodies on Colo320 and Colo741 cells after quercetin application

	Colo320 cell		Colo741 cell	
	Control group	Quercetin	Control group	Quercetin
Dicer	121.3±15	171.4±40.6**	277.5±33.3	325±50
eIF2α	214.3±38.4	211.2±41.6	365±19.15	275±86.6*
Ago2	107.2±6.97	102.5±5	127.5±32	110.4±12.5
CD9	107.5±9.5	108.8±4.7**	112.5±25	192±21.4*
CD63	173.8±19.6	197.7±10.4**	124.2±48	115±19.15

*Significant data after comparison with control group.
**Significant data after comparison with Colo-741 group

Discussion

CRC is associated with high mortality due to its low early detection rate owing to the lack of early-stage symptoms, and due to metastasis in the late stage. Given these diagnostic and clinical challenges, new approaches are promptly needed to diagnose effectively and improve the outcome of patients. Recent studies demonstrated that the TME played role in tumor progression and response of colorectal cancers to the therapy (27). Also, experimental data have indicated that exosomal proteins and/or miRNAs can influence this gastrointestinal malignancy at various stages (28). According to the study results of Dong et al. (29), the exosomes originating from tumoral cells affect tumor progression, formation, and metastasis. The results also show that especially specific exosomal miRNAs may play a vital role in the tumoral network. These clinical findings show the potential therapeutic effects of the regulation of exosomal miRNA secrationv (29). Besides, exosomes can improve CRC progression by elevating tumor cell proliferation via changing particular essential regulatory genes and controlling several molecular signaling pathways (30).

According to surveillance, epidemiology, and databases, the 5-year survival percentage of patients with CRC is 64%.

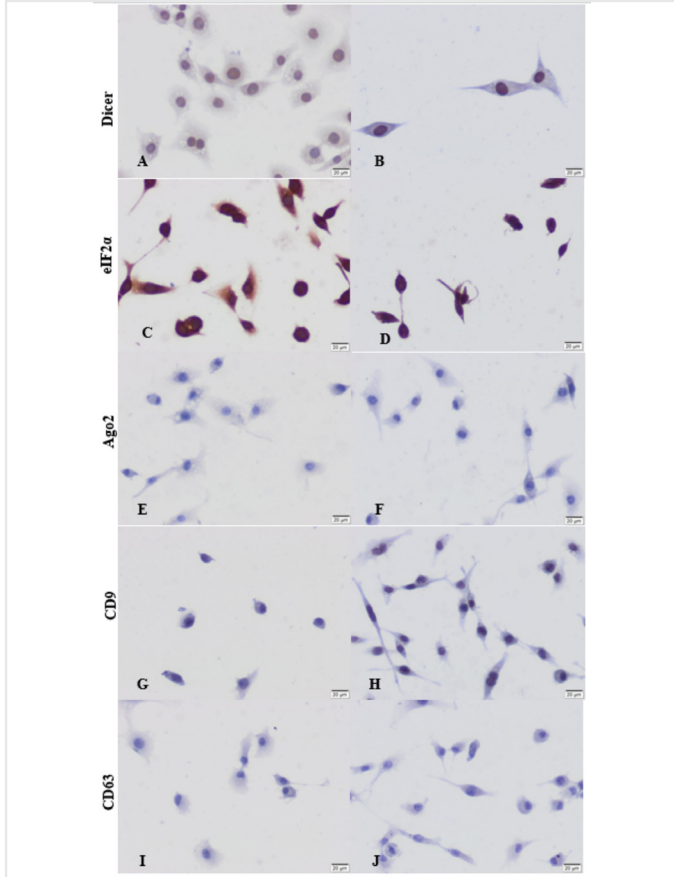

Figure 3. Dicer (A, B), eIF2α (C, D), Ago2 (E, F), CD9 (G, H), CD63 (I, J) immunoreactivity in control (A, C, E, G, I) and 25 μM quercetin-applied (B, D, F, H, J) Colo741 cells. Morphological changes were observed in the cells after quercetin application. Scale bars = 20 μm

Surgical intervention, chemotherapy, and radiotherapy are the most common treatment methods for CRC (31). The effects of natural polyphenolic compounds on CRC cells were searched and it was suggested that they could inhibit the carcinogenesis process by triggering of cell death signaling pathways or diverse molecular mechanisms. Quercetin, which is primarily found in apples, onions, strawberries, and red wine, is a natural polyphenolic compound and is the most commonly studied polyphenolic compound on cancer cells (32).

Previously, it was reported that quercetin inhibited the viability and proliferation of cancer cells. On the B16F10 (melanoma cell line), 5μM quercetin reduced cellluar viability (33). In addition, 20 μM quercetin also affected viability of SW- 620 and Caco- 2 cells (34). Another experimental study reported that the viability of Caco- 2 cells was inhibited after quercetin (20 μM for 24h) application (35). According to our study, the effective quercetin dosage was 25 μg/mL for 48h in Colo320 and Colo741 cells (24).

Exosomes are nano-sized and membrane-bound vesicles that are crucial components of the TME. Also, exosomes, proteins, and exosomal miRNAs originating from cancer cells may control the progression or survival of CRC cells. Accordingly, there has been increased interest in micro-stuffed molecules found in exosomes as possible cancer cell biomarkers, and targets for CRC (5). Also, these microvesicles transfer mRNAs, miRNAs, fragments of DNA, and proteins from active cancer cells to distant cells (36). In the first decade, accumulating evidence showed that different protein and miRNA contents in the plasma exosomes of patients might be beneficial prognostic biomarkers and would encourage the specification of new therapeutic strategies in CRC (37,38). Although polyphenolic compounds can potentially affect CRC prognosis by affecting miRNA concentrations, this effect may differ in Colo320 primary and Colo741 metastatic cell lines. Accordingly, our experimental showed increased miRNA concentrations in Colo741 cells after quercetin administration. This increase was not statistically significant.

In the present study, we showed that the Dicer and eIF2α immunoreactivities were higher in Colo741 cells than in Colo320 cells. After quercetin application, Dicer immunoreactivity was highest; in contrast, eIF2α immunoreactivity decreased after quercetin application, especially in Colo741 cells. Metastatic colon adenocarcinoma cells are more aggressive than primary cells, and survival and response to the therapy are worse than primary cancer cells. Therefore, therapeutic strategy for primary and metastatic CRC should be different. While CD9 immunoreactivity was statistically significantly higher in quercetin-applied Colo741 cells, CD9 immunoreactivity was similar in both Colo320 and control Colo741 cells. However, the CD63 immunoreactivity was elevated in Colo320 cells and reduced in the Colo741 cells after the quercetin application. Therefore, quercetin may trigger exosome secretion from Colo320 cells.

miRNAs are small non-conding RNAs that are differentially expressed and arrange various cellular pathways. Molecular studies suggested that miRNAs had crucial roles in CRC progression and metastasis, therefore, miRNAs could be a strong biomarker for CRC diagnosis. Recent evidence indicated that the biogenesis of miRNAs and related proteins, including Ago2 and Dicer, affected several cancers' development. While deletion of the Dicer gene locus d was associated with pre-cancerous lesions and cancer cell invasion in lung adenocarcinomas (39), and elevated expression of Dicer protein was related to poor prognosis in CRC (18,40), and colon cancer stem cells (41), the Dicer-related molecular mechanism involved in CRC was still unclear.

Our results suggested that the Dicer immunoreactivity was elevated in both quercetin applicated Colo320 and Colo741 cells compared to control groups. Furthermore, increased and significant Dicer immunoreactivity was detected in quercetin applied Colo741 cells compared to quercetin applied Colo320 cells. Thus, quercetin could upregulate tumor suppressive miRNA and have protective effects in CRC by increasing the expression of Dicer.

Ago2 protein is a key and essential regulator of miRNAs secretion. Overexpression of Ago2 has been found in CRC, ovarian, and gastric carcinoma cells (42-44,14). Feng et al. (45) showed that elevated Ago2 was associated with cancer aspects such as its cell growth, proliferation, and also survival of patients. The upregulation of Dicer mRNA expression was not positively correlated with mRNA expression levels of Ago2 (46). Our results demonstrated that the immunoreactivity of Ago2 decreased but this decrease was not significant in both quercetin applied Colo320 and Colo741 cells compared with control groups. The Ago2 changes should be examined at mRNA levels before and after quercetin administration in both type of cells.

Recent experimental studies prescribed that quercetin could reveal conspicuous endoplasmic reticulum stress in different cancer cell types (47,48). The other cellular stress type leads to inhibition of cell translation, which is thought to encourage survival and save energy. In eukaryotic cells, the best-characterized inhibition mechanism of translation regulation is the phosphorylation of eukaryotic initiation factor eIF2α. Additionally, translational attenuation can induce autophagy and apoptosis in cells (49). Accordingly to our data, the eIF2α staining intensities were decreased in both Colo320 and Colo741 cells after quercetin administration, but significant decrease was only detected in the Colo741 cells. In another publication, we showed quercetin initiated cell death in Colo320 and Colo741 cells, which was in line with the results of this study (24). Our results demonstrated that quercetin might have preventive effects by inhibiting the eIF2α protein expression and stimulating cell death in Colo741cells.

miRNAs are single small stand noncoding RNA molecules that inhibit the translation of mRNA and induce degradation

of mRNA. Moreover, experimental miRNA studies reported that varying miRNA levels might regulate tumor formation in CRC (9). According to our exosomal total miRNA levels, they were elevated in Colo320 and Colo741 cells after quercetin administration, but the increase was not statistically significant.

Study Limitations

The present study used a total miRNAs analysis kit to define the exosomal miRNA concentrations in CRC cell lines after quercetin application. This miRNA analysis can be done with commercial kits that determine the specific miRNAs that affect the pathogenesis and may change concerning the cancer type. Finally, to define the exact anti-cancer properties and activities of quercetin on CRC cells. Furthermore, assessment with various mechanisms and various signaling pathway molecules that include probable carcinogenesis mechanisms is necessary.

Conclusion

In conclusion, using five different doses, we showed the anti-cancer effects of quercetin in Colo320 and Colo741 cells. Accordingly, quercetin increased CD9 exosomal biomarker expressions in Colo741 cells. Moreover, high Dicer and exosomal miRNA levels in both two Colo320 and Colo741 cell lines showed the effectivity of quercetin. These results suggest that reduced eIF2α immunoreactivty may be associated with the quercetin-stimulated apoptosis in Colo741 cells. However, proteins that were related with exosomal proteins or miRNAs were similar in Colo320 and Colo741cancer cells before and after quercetion application.

In the current study, we showed that CD9 immunoreactivity elevated significantly in quercetin-administrated Colo741 cells compared to the control group. Moreover, CD9 immunoreactivity was lower and this decrease was significant in Colo320 cells than in Colo741 cells after the application of quercetin. Otherwise, after quercetin application, CD63 immunoreactivity was elevated in Colo320 cells and decreased in Colo741 cells. The increase in CD63 immunoreactivity was statistically significant in quercetin-administrated Colo320 cells compared with quercetin-administrated Colo741 cells. We concluded that secretion of exosomes occurred in response to the quercetin administration in both primer and metastatic colon cancer cell lines, therefore, exosomes and their surface proteins, CD63 and CD9, could be used for colon carcinoma identification.

Ethics

Ethics Committee Approval: Colo-320 (ATCC: 220.1) primary and COLO-741 (ECACC: 93052621) metastatic colon cancer cell lines were used in our study. Therefore, the study does not require ethics committee approval.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Concept: E.B., H.S.V., Design: E.B., S.Ö., H.K., Data Collection or Processing: H.K., H.S.V., Analysis or Interpretation: E.B., H.K.E, H.S.V., Literature Search: E.B., S.Ö., Writing: E.B., S.Ö., H.S.V.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

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Determining the Frequency of Restless Legs Syndrome in the Adult Population

Erişkin Popülasyonda Huzursuz Bacak Sendromu Sıklığının Belirlenmesi

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ABSTRACT

Objective: Restless legs syndrome (RLS) is a chronic disease that usually occurs in the legs, resulting in involuntary movement of the legs with uncomfortable sensations. RLS negatively affects the quality of life of individuals. In this study, it is aimed to increase awareness by determining the frequency of RLS in the adult population.

Methods: The study was a descriptive and cross-sectional study. In the study, 565 individuals aged 18 and over participated. The data were collected online from individuals with the form of describing the personal characteristics of the individuals, the RLS Diagnostic Criteria Questionnaire, and the RLS Severity Rating Scale. IBM SPSS statistics 26.0 program was used in the analysis of the data.

Results: In this study, the frequency of RLS was 17.5% and the severity score was 19.22±6.97 (moderate). The rate of admitting to a health institution due to the symptoms of individuals is 5.8%. In this study, the frequency of RLS was found to be significantly higher in those with diabetes, hypertension, age, and high body mass index.

Conclusion: Although most of the participants in this study had symptoms of RLS, it was seen that they were not admitted to a health institution. If these individuals are not treated, their quality of life gets affected negatively, and this negatively affects the quality of health care. In order to increase the quality of health care, RLS should be screened especially in risky groups and treatment should be started in determined patients.

Keywords: Care, restless legs syndrome, population, prevalence

ÖZ

Amaç: Huzursuz bacak sendromu (HBS), genellikle bacaklarda oluşan, rahatsızlık verici hislerle birlikte bacakları istem dışı oynatma durumuyla ortaya çıkan kronik bir hastalıktır. Bu hastalık bireylerin yaşam kalitesini olumsuz şekilde etkilemektedir. Bu çalışmada, erişkin popülasyonda HBS sıklığının belirlenerek farkındalığın artırılması amaçlamaktadır.

Yöntemler: Çalışma tanımlayıcı ve kesitsel bir araştırmadır. Çalışmaya 18 yaş ve üzeri 565 birey katılmıştır. Veriler bireylerden; bireylerin kişisel özelliklerini tanımlama formu, HBS Tanı Kriterleri Anket Formu ve HBS Şiddeti Derecelendirme Skalası ile online olarak toplanmıştır. Verilerin analizinde IBM SPSS statistics 26.0 programı kullanılmıştır.

Bulgular: Bu çalışmada HBS sıklığının %17,5, HBS şiddetinin ise 19,22±6,97 (orta düzey) olduğu belirlenmiştir. Bireylerin belirtilerinden dolayı sağlık kuruluşuna başvurma oranı %5,8 idi. Bu çalışmada diyabeti, hipertansiyonu, yaşı ve vücut kitle indeksi yüksek olanların HBS sıklığı anlamlı şekilde daha yüksek bulunmuştur.

Sonuç: Bu çalışmada katılımcıların büyük bir kısmında HBS belirtileri görülmesine rağmen, katılımcıların çoğunun bir sağlık kuruluşuna başvurmadığı görülmektedir. Bu bireyler tedavi edilmediği takdirde yaşam kaliteleri olumsuz olarak etkilenmekte ve bu durum da sağlık bakım kalitesini negatif etkilemektedir. Sağlık bakım kalitesinin yükselmesi için HBS'nin özellikle riskli gruplarda taranması ve belirlenen olgularda tedavisinin başlanması gerekmektedir.

Anahtar Sözcükler: Bakım, huzursuz bacak sendromu, popülasyon, prevalans

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Introduction

Restless legs syndrome (RLS) is a chronic disease that usually occurs in the legs, resulting in involuntary movement of the legs with uncomfortable sensations. In this syndrome, symptoms occur mostly at night and when individuals go to resting state, they decrease or temporarily improve with movement and walking (1). RLS can occur primarily with genetic transmission, and secondarily in conditions such as drug use, caffeine consumption, Parkinson's disease, diabetes, fibromyalgia, hypothyroidism, multiple sclerosis, end-stage kidney disease, iron deficiency anemia, and pregnancy (2). Although RLS, which is common in society, is a treatable disorder, it cannot be adequately defined by clinicians and therefore cannot be treated (3). Studies indicate that 5-15% of the population may have RLS (4). Since symptoms occur at night and at rest in individuals, they significantly affect sleep, decrease quality of life, increase psychological disorders such as depression and anxiety, decrease work efficiency, and cause social and economic burden (5,6). RLS has an important place in the health care discipline in terms of holistic evaluation of the patient, as it negatively affects the quality of life of individuals. Although there are studies on RLS in the literature, there is a need for new studies that will raise awareness because it is common in the society (4). This study aims to increase awareness by determining the frequency of RLS in the adult population.

Methods

Study Design

The study was descriptive and cross-sectional.

Sample of the Research

The sample of the study consisted of 565 individuals aged 18 and over who voluntarily agreed to participate in the study. They were informed about the research and their rights, and their "informed consent" was obtained before the research. All the rights of the participants were respected and the principles of voluntariness and confidentiality were paid attention to.

Data Collection Method

Data were collected by online survey method between 09 May and 09 June 2023.

Data Collection

While collecting the data, a form describing the personal characteristics of the individuals, the RLS Diagnostic Criteria Questionnaire Form and the RLS Severity Rating scale were used.

Personal Characteristics Identification form of Individuals

The form was created by scanning the literature. It was a 13-item questionnaire including the following questions: age, gender, educational status, height, weight, presence of any additional disease, whether the patient consumed more than a glass in total from drinks such as tea, coffee, instant coffee, cola, cold tea, whether the patient engaged in activities such as regular exercise, walking, yoga, and relaxation exercises for at least 30 minutes in his/her spare time apart from his/her work, smoking and alcohol use, presence of hypertension, being overweight, and whether the patient was admitted to a health institution due to his/her complaints.

Restless Legs Syndrome Diagnostic Criteria Questionnaire form (RLSDCQF)

The diagnostic form was created by the International RLS Working Group in 1995 based on the patient's history. The form consists of 5 questions. RLS is diagnosed by answering "yes" to all questions in the form (7). The reliability and validity study of the form in Turkey was performed by Sevim et al. (8), and it was reported that the cronbach alpha coefficient of each item was greater than 0.81.

Restless Legs Syndrome Severity Rating Scale (RLSRS)

The scale was developed by the International RLSWorking Group. The scale consists of 10 questions. RLS severity values in each question are graded as no effect of RLS (0 points) or very severe effects (4 points). Thus, a total score ranging between 0 and 40 is obtained; A score of 1-10 indicates mild disease, a score of 11-20 indicates moderate disease, a score of 21-30 indicates severe, and a score of 31-40 indicates very severe disease. The RLSRS is a scale that has been used in many studies in our country and has been shown to be valid and safe (9-11). The scale was adapted in our country by Ay et al. (12), and the cronbach alpha value was found to be 0.89. In this study, the cronbach alpha value was found to be 0.887.

Statistical Analysis

IBM SPSS statistics 26.0 program was used for statistical analysis in the study. While evaluating the study data, in addition to descriptive statistical methods (mean, standard deviation, frequency, percent), the Student's t-test was used to compare normally distributed data, and the Mann-Whitney U test was used to compare data that did not show normal distribution. The chi-squared test was used to evaluate the relationships between the variables. The results were evaluated at the 95% confidence interval and the significance level of $p<0.05$.

Ethical Aspect of the Study

Before starting the study, permission obtained from the Ethics Committee of İstanbul Gelişim University with the date of 19.04.2023 and the decision number 2023-04-87. Permission was obtained from the scale's authors. Participants who voluntarily accepted to participate in the study were informed about the research and their rights as necessary, and their "informed consent" was obtained before the research. All the rights of the participants were respected and the principles of voluntariness and confidentiality were paid attention to.

Results

The personal characteristics of the individuals participating in the study are shown in Table 1. It was determined that 65.8% of the participants were women, 51.3% were university graduates,

Table 1. Personal characteristics of individuals and the frequency and severity of restless legs syndrome (n=565)

	n	%
Gender		
Male	193	34.2
Female	372	65.8
Age (mean)	37.68±12.07	
Body mass index (mean)	26.09±4.82	
Educational status		
Literate	17	3.0
Primary school graduate	43	7.6
Secondary school graduate	32	5.7
High school graduate	183	32.4
Graduated from a university	290	51.3
Those with diabetes	41	7.3
Those with COPD	6	1.0
Those with cardiovascular disease	22	3.9
Those with chronic kidney failure	1	0.2
Those treated for vitamin B12 deficiency (in the last 1 year)	77	13.6
Those treated for iron deficiency (in the last 1 year)	81	14.3
Those receiving treatment for Mg deficiency (in the last 1 year)	21	3.7
Those with hypertension or those who are overweight	214	37.9
Those with other comorbidities	82	14.5
Those who consume beverages such as tea, coffee, cola, cold tea more than 1 glass a day	426	75.4
Those who do activities such as exercise, walking, yoga, relaxation exercises for at least 30 minutes a day while working or at home, apart from routine work.	146	25.8
Smokers	185	32.7
Alcohol users	84	14.9
Those with RLS	99	17.5
Those who are admitted to any health institution due to symptoms	33	5.8
Total severity score in patients with RLS (mean)	19.22±6.97	

Descriptive statistical methods (mean, standard deviation, frequency, percent).
RLS: Restless legs syndrome

and the mean age was 37.68±12.07. While the mean body mass index (BMI) of the individuals was found to be 26.09±4.82 and the rate of being hypertensive or overweight was 37.9%. (Table 1). The rate of those who consumed more than 1 glass of beverages such as tea, coffee, cola, and cold tea per day was 75.4%, the rate of those who did activities such as exercise, walking, yoga, relaxation exercises for at least 30 minutes a day outside of their routine work or at home was only 25.8%, the rate of those who smoked was 32.7%, and the rate of alcohol users was 14.9% (Table 1). As a result of the RLSDCQF, RLS was diagnosed in 99 (17.5%) of 565 individuals and applied the mean score in RLSRS was determined as 19.22±6.97 (moderate level). The mean scores of RLS severity were compared between male and female genders and no significant relationship was found (p=0.692). Thirty-three (5.8%) of the participants were admitted to a health institution due to RLS symptoms. (Table 1).

The relationship between the personal characteristics of the participants and RLS is shown in Table 2. A significant correlation was found between the individuals' age, BMI and RLS ($p<0.05$). RLS increased as age and BMI increased. A significant relationship was found between the education levels of the individuals, the presence of diabetes and hypertension, and RLS ($p<0.05$).

Discussion

In this study, RLS was found in 17.5% of the adult population, and the mean score was 19.22±6.97 (moderate level), as a result of RLSRS applied to those with RLS (n=99) (Table 1). In the study conducted by Demirci and Şahin (13) with 447 university students with an average age of 20.3±1.76 years, it was determined that 7.6% of the students had RLS and the mean severity was 13.1±5.44. In studies conducted in various patient groups in our country, the incidence of RLS was between 8% and 30% (14-16), and in studies conducted with individuals without any

disease, the frequency was between 2% and 9% (17-19). In the study conducted by Phillips et al. (3), it was determined that the frequency of RLS was 10% and increased with age. In this study, similar results were found with the literature. In the study, RLS was found to be higher in groups with diabetes and hypertension. In the literature, the results of the studies conducted in similar patient groups are similar to this study.

In the study, no significant relationship was found in terms of RLS between those who received treatment for iron, B12 and Mg deficiencies in the last 1 year and those who did not have iron, B12 or Mg deficiency (p>0.05). RLS can be passed on primarily through genetic inheritance, or it can occur secondary to drug use, caffeine consumption, Parkinson's, diabetes, fibromyalgia, hypothyroidism, multiple sclerosis, end-stage kidney disease,

Table 2. The relationship between personal characteristics of individuals and restless legs syndrome (n=99)

	n	p
Gender		
Male	33	0.907
Female	66	
Age		
Average age of patients with RLS	42.79±10.35	**0.001**
Mean age of those without RLS (n=466)	36.59±12.14	
BMI		
Mean BMI of those with RLS	27.64±5.25	**0.001**
Mean BMI of those without RLS (n=466)	25.76±4.67	
Educational status		
Literate	2	**0.019**
Primary school graduate	15	
Secondary school graduate	8	
High school graduate	28	
Graduated from a University	46	
Consumption of beverages such as tea, coffee, cola, cold tea more than 1 glass a day		
Yes	81	0.209
No	12	
Sometimes	6	
The state of doing activities such as exercise, walking, yoga, relaxation exercise for at least 30 minutes a day outside of routine work or at home		
Yes	22	0.494
No	58	
Sometimes	19	
Presence of diabetes		
Those with diabetes	15	**0.001**
Non-diabetic individuals	84	
B12 deficiency treatment (in the last 1 year)		
Those treated for B12 deficiency	17	0.258
Those without B12 deficiency	82	
Status of receiving iron deficiency treatment (in the last 1 year)		
Those receiving treatment for iron deficiency	16	0.568
Those without iron deficiency	83	
Receiving Mg deficiency treatment (in the last 1 year)		
Those treated for Mg deficiency	7	0.051
Those without Mg deficiency	92	
Presence of hypertension		
Those with hypertension	14	**0.033**
Those without hypertension	85	

Descriptive statistical methods (mean, standard deviation, frequency), Student's t-test, Mann-Whitney U test ,The chi-squared test. RLS: Restless legs syndrome

iron deficiency anemia, and pregnancy (2). In the case report of Sayin and Atilla (20), it was found that iron deficiency increased the symptoms of RLS, and in the study conducted by Çetinkaya et al. (15), the frequency of RLS was 12.5% in patients with iron deficiency anemia. The result of this research is not similar to the literature. In this study, those treated for iron deficiency, B12 or Mg deficiencies in the last 1 year were included in the sample. Treatments taken by individuals during this period may have eliminated iron, B12 and magnesium deficiencies and may have been effective in reducing the symptoms of RLS causing discomfort. Therefore, the results may differ from the literature.

In this study, a significant relationship was found between the education levels of individuals and RLS ($p<0.05$). When statistical analysis was examined in detail, primary school graduates had higher rate of RLS. The mean age of primary school graduates (51.02±10.54) was higher than other graduates. A significant correlation was found between age and the frequency of RLS ($p<0.05$). According to this analysis, although being a primary school graduate did not directly affect the rate of RLS, it may have affected the rate of RLS indirectly due to higher average age.

Study Limitations

In the study, a significant relationship was found between BMI and RLS ($p<0.05$). The rate of RLS was higher in those with higher BMI. Both age and BMI were found to be higher in patients with RLS compared to those without RLS. According to this result, as the age increased in patients with higher BMI as in primary school graduatesthe rate of RLS also increased.

Conclusion

As a result, it was determined that the frequency of RLS in the adult population was 17.5% and the severity was 19.22±6.97 (moderate level). Although 17.5% of the participants had symptoms, only 5.8% of them were admitted to a health institution because of the symptoms. RLS can be treated when detected. However, as a result of the study, it was determined that a high rate of patients was not admitted to a health institution. The life quality of individuals who cannot be treated will be adversely affected by these symptoms. In this study, the rate of RLS was found to be significantly higher in those with diabetes, hypertension, older age, and higher BMI. The negative impact on the quality of life of individuals also negatively affects the quality of health care. In order to increase the quality of health care, RLS should be screened especially in risky groups and treatment should be started in determined patients.

Ethics

Ethics Committee Approval: Before starting the study, permission obtained from the Ethics Committee of İstanbul Gelişim University with the date of 19.04.2023 and the decision number 2023-04-87. Permission was obtained from the scale's authors.

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Authorship Contributions

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Original Article

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Effect of Different Polymerization Times on the Microhardness and Intrapulpal Temperature of Glass Ionomers

Farklı Polimerizasyon Sürelerinin Cam İyonomerlerin Mikrosertliği ve Pulpaiçi Isı Artışı Üzerine Etkisi

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ABSTRACT

Objective: The aim of this study was to compare the microhardness of high viscosity glass ionomer, glass carbomer (GC) and bioactive restorative material (BRM) exposed to different polymerization times, and the intrapulpal thermal changes they caused on teeth.

Methods: Sixty human molar teeth were used in this study. During Class I cavity preparation,1 mm dentine thickness was left between the pulp chamber and occlusal cavity floor.Teeth were randomly divided into six groups. Group 1: restored with high viscosity glass ionomer cement (HV-GIC), cured for 20 sec., Group 2: restored with HV-GIC, cured for 40sec., Group 3: restored with conventional glass ionomer cement, cured for 60 sec., Group 4: restored with GC and cured for 90 sec., Group 5: restored with BRMs, cured for 20 sec., Group 6: restored with BRM, cured for 40 sec. All glass ionomer cements were polymerized with a LED light curing unit except GC groups. GC groups were cured with a special thermocure lamp. As soon as the materials were placed in the cavities, temperature increase on the tooth during setting/polymerization reactions were measured with a thermocouple wire connected to a data logger. All of the specimens were polished with discs.Then, microhardness values were evaluated from three different points. Data were analyzed using one-way ANOVA, Tukey test and paired t-tests ($p<0.05$).

Results: Group 2 showed statistically significantly higher increase in temperature when compared to Group 1. Group 4 showed statistically significantly higher temperature than Group 3. There

ÖZ

Amaç: Bu çalışmanın amacı, farklı polimerizasyon sürelerine maruz bırakılan yüksek viskoziteli cam iyonomer, cam karbomer (GC) ve biyoaktif restoratif materyalinin (BRM) mikrosertliklerini ve intrapulpal termal değişiklikleri karşılaştırmaktır.

Yöntemler: Bu çalışmada 60 adet çekilmiş molar dişi kullanıldı. Sınıf 1 kavite preparasyonu sırasında pulpa odası ile oklüzal kavite tabanı arasında 1 mm dentin kalınlığı bırakıldı. Dişler rastgele altı gruba ayrıldı. Grup 1: Yüksek viskoziteli cam iyonomer siman (HV-GIC) ile restore edildi, 20 sn polimerize edildi. Grup 2: HV-GIC ile restore edildi, 40 sn polimerize edildi. Grup 3: GC ile restore edildi, 60 sn polimerize edildi, Grup 4: GC ile restore edildi ve 90 sn polimerize edildi. Grup 5: Biyoaktif restoratif materyal (BRM) ile restore edildi, 20 sn polimerize edildi, Grup 6: BRM ile restore edildi, 40 sn polimerize edildi. GC grupları hariç tüm cam iyonomer simanları LED polimerizasyon cihazı ile polimerize edildi. GC grupları özel ışık aleti ile polimerize edildi.Tüm örneklerin pulpaiçi ısı artış değerleri J tipi termometre cihazı ile ölçüldü. Daha sonra mikrosertlik değerleri üç farklı noktadan değerlendirildi. Veriler tek yönlü ANOVA, Tukey testi ve t-testleri ile analiz edildi ($p<0,05$).

Bulgular: Grup 2, Grup 1'e göre pulpaiçi ısı artışında istatistiksel olarak anlamlı fark gösterdi Grup 4, Grup 3'e göre istatistiksel olarak daha yüksek pulpaiçi sıcaklık artışı gösterdi. Gruplar karşılaştırıldığında en yüksek mikrosertlik değerleri GC gruplarında elde edildi. Grup 2, Grup 1'e göre istatistiksel anlamlı derecede

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ABSTRACT

was no significant difference between Groups 5 and 6 in terms of temperature changes. The highest microhardness values were obtained in GC groups, when the groups were compared to each other. Group 2 showed significantly higher microhardness value than Group 1. Group 6 showed significantly higher microhardness values than Group 5.

Conclusion: Fourty sec polymerization of the BRM positively affected the microhardness without causing an intrapulpal temperature increase. While high microhardness values were obtained in 90 sec polymerization of GC, it also caused an increase in temperature that would damage the pulp.

Keywords: Glass-ionomer, microhardness, intrapulpal, bioactive, carbomer

ÖZ

yüksek mikrosertlik değeri gösterdi. Grup 6, Grup 5'e göre anlamlı derecede yüksek mikrosertlik değeri gösterdi.

Sonuç: BRM'nin 40 sn polimerizasyonu intrapulpal sıcaklık artışına neden olmadan mikrosertliği olumlu yönde etkilemiştir. GC'nin 90 sn polimerizasyonunda yüksek mikrosertlik değerleri elde edilirken pulpaya zarar verecek derecede ısı artışına da neden olmuştur.

Anahtar Sözcükler: Cam iyonomer, mikrosertlik, pulpaiçi, biyoaktif, karbomer

Introduction

Resin-containing materials are commonly preferred in restorative dentistry due to their high mechanical and esthetic properties. However, the cytotoxic effects of the monomers that release on the pulp tissue and the applications requiring technical sensitivity, have led to the search for new materials in the field of restorative dentistry (1).

Conventional glass ionomer materials are one of the most frequently researched and developed restorative materials. Glass carbomer (GC) (GC Dental, Netherlands) is one of the=new glass ionomer-based materials. GC contains nano-fluorapatite and nano-hydroxyapatite particles differently from the conventional glass ionomer cements (CGICs) (2). Containing nano-particles is believed to promote remineralization of caries-affected dentin and enamel (3). Besides, the incorporation of nano-particles provides better mechanical and chemical properties to GC when compared to CGICs (2). Actually, the clinical application procedures of GC are similar to CGICs, with the exception that heat application is recommended during the setting reaction for GC (4). Although the application of high energy polymerization unit, GC sets with an acid-base reaction chemically (3). And the use of heat is supposed to accelerate the matrix-forming reaction of GC (4). The recommended polymerization time for GC is between 60 and 90 sec (5).

High viscosity glass ionomer cements (HV-GICs) are another newly developed CGICs (Equia Fil, GC Dental Co., Tokyo, Japan). One of the main differences between HV-GICs and CGICs are the ratio of the particles and the size of the particles (6). HV-GICs have improved physical, mechanical, and esthetic properties and are less sensitive to moisture when compared with the CGICs (7,8). Equia Fil is advised to be used with a novel nanofilled coating material (Equia Coat, GC Dental Co., Tokyo, Japan) which protects the material against wearing in the oral environment (9). Coating material should be applied with heat application. Thus, the mechanical properties of Equia Fil are also improved.

Bioactive restorative material (BRM) (Pulpdent Corporation, Watertown, USA) is one of the preferred materials containing no Bisphenol A, BIS-GMA, or BPA derivates. BRM is a resin-modified glass ionomer cement (RMGIC) reinforced with rubberized resin (10). BRM showed similar flexural strength and flexural fatigue with flowable composites (10). Also, BRM demonstrated similar mechanical properties to bulk-fill resin composites (11).

Heat application is one of the operative procedures that can damage pulp tissue (2). Zach and Cohen stated that a 5.5 °C increase in the intrapulpal temperature can cause irreversible damage to the pulp (11,12). *In vitro* studies have pointed out that different light sources used during the polymerization of resin-based restorative materials may cause such an increase in the pulp temperature (11,12). In addition, thermal conduction is affected by the thickness of the remaining dentin tissue (13). It has been mentioned that remaining dentin thickness has an essential role in preserving the vitality of the pulp (14).

Studies exhibited that increasing the polymerization time may improve the mechanical properties of a material 15-18). However, there is no study evaluating the influence of extended polymerization time on the intrapulpal temperature and mechanical properties of glass ionomers materials.

Therefore, this study aimed to compare the microhardness of HV-GICs, GC, and BRM polymerized at different times and evaluate the intrapulpal thermal changes during increased polymerization times.

The null hypothesis of the study are;

1. The microhardnesses of HV-GICs, GC, and BRM do not differ depending on the different polymerization times.

2. Intrapulpal thermal changes do not differ depending on the increased polymerization time applied on hV-GICs, GC, and BRM.

Methods

Tooth Selection and Preparation

Sixty extracted, caries-free human molars were stored in 0.5% Chloramine T solution until the test started. Class I cavities (2 mm widht, 2 mm depth, 3 mm length) were prepared with diamond burs (G&Z Instruments, Austria). 1 mm dentin thickness that was measured with a digital micrometer was left between the pulp chamber and occlusal cavity floor. After cavity preparations, the roots of each tooth were removed. Then, all teeth were randomly divided into six subgroups (n=10):

Group 1: Equia Fil + Light emitting-diode (LED) curing light (VALO Cordless, Ultradent, South Jordan, Utah) 20 sec.

Group 2: Equia Fil + LED curing light 40 sec.

Group 3: GC + GC CarboLED thermocure lamp (Carboled, GC Dental Netherlands) 60 sec.

Group 4: GC + GC CarboLED thermocure lamp 90 sec.

Group 5: BRM + LED curing light 20 sec.

Group 6: BRM + LED curing light 40 sec.

Materials used in this study are provided in Table 1.

Bezmialem Vakıf University Non-invasive Research Ethics Committee (number: E-54022451-050.01.04-7929/date: 20.03.2021).

Restoration Procedures

Group 1: Capsulated HV-GICs, Equia Fil, was mixed for 10 sec. The mixture was applied to the cavity in bulk immediately. After 2 min 30 sec, the Equia Coat was applied and cured for 20 sec.

Group 2: Capsulated HV-GICs, Equia Fil, wasmixed for 10 sec. The mixture was applied to the cavity in bulk immediately. After that, the Equia Coat was applied and cured for 40 sec.

Group 3: GC capsule was mixed for 15 sec with its mixer (GC Dental, Netherlands). GC material was placed in the cavity in a single increment. After the cavity was filled, the surface cover with silicone was applied to the cavity and condensed with finger pressure. Finally, it was polymerized with a CarboLED light device set at a power of 1,400 mW/cm^2 for 60 sec.

Group 4: GC capsule was mixed for 15 sec with its mixer. GC material was placed in the cavity in a single stage. After the cavity was filled, the surface cover with silicone was applied to the cavity and condensed with finger pressure. Finally, it was polymerized with a CarboLED light device set at a power of 1,400 mW/cm^2 for 90 sec.

Group 5: Cavities were selectively etched with 37.5% phosphoric acid (Ultradent, South Jordan, USA) for 15 sec, rinsed with water, and dried. Later, BRM was placed into the cavity using a syringe, according to the manufacturer's instruction with the bulk technique. Finally, the samples were polymerized with LED light curing unit (Ultradent, South Jordan, Utah, USA) for 20 sec.

Group 6: Cavities were selectively etched with 37.5% phosphoric acid for 15 sec, rinsed with water, and dried. Later, BRM was placed into the cavity using a syringe, according to the manufacturer's instruction with the bulk technique. Finally, the samples were polymerized with LED light curing unit for 40 sec.

The Experimental Design and Measurement of Intrapulpal Temperature

The pulpal microcirculation model was demonstrated in Figure 1, designed by Savas et al. (19).

A thermal gel (Hutixi, HTGY 260, China) was injected into the pulp chamber to facilitate heat transfer from the roof of the pulp chamber to the thermocouple. As soon as the materials were placed in the cavities, temperature increases in the tooth during setting/polymerization reactions were measured with a j type-thermocouple (Fluke 54 II, Washington, USA) connected to a data logger. For all specimens, initial and highest temperature values were recorded. In addition, differences between initial and highest temperatures were determined (Δt) (19).

Table 1. Materials used in this study

Material	Manufacturer	Chemical composition
GCP (Glass Carbomer Cement) GCP Gloss	GCP Dental, Netherlands	Floraluminosilicate glass, apatite, polyacid Modified polysiloxanes
Equia Fil (High Viscosity Glass Ionomer) Equia Coat	GC, Tokyo, Japan	Floraluminosilicate glass, carboxylic acid, polyacrylic acid, water Methyl methacrylate, colloidal silica,camphorquinone, urethane methacrylate, phosphoric ester monomer
Activa Bioactive (Bioglass-reinforced Glass Ionomer Cement)	Pulpdent, USA	Mix of methacrylates and diurethane with modified polyacrylic acid; reactive glass Filler; inorganic filler, rubberized resin, Water
GCP CarboLED Valo Cordless (standart mode)	GCP Dental, Netherlands Ultradent, South Jordan, Utah, USA	1,400 mW/cm^2 power out-put 1,000 mW/cm^2 wavelenght 480 nm

Measurement of Microhardness Values

The specimens were polished with discs (Sof-Lex, 3M ESPE, USA) from coarse to fine. Then, microhardness values were evaluated from three different points by applying a load of 200 g for 10 sec on top surfaces using a micro Vickers hardness test machine (Shimadzu, Japan).

Statistical Analysis

The sample size was calculated at the significance level of 0.05 and power of 0.90 using G*Power v3.1 (Heinrich Heine, Universitat Dusseldorf, Dusseldorf, Germany). Statistical analysis of the data was performed by one-way ANOVA, Tukey, and paired t-tests. A p value of <0.05 was considered to be statistically significant.

Results

Group 2 (±4.49) showed a significantly higher increase in pulpal temperature than Group 1 (±3.29) (p=0.018). For Group 4, temperature increases over 5.5 degrees were observed. However, the highest temperature increase was calculated in Group 4 (±6.72) when polymerized for 90 sec. Group 4 showed a significantly higher increase in pulpal temperature than Group 3 (±5.49) (p=0.040). There were no significant differences between Group 5 (±3.95) and Group 6 (±4.48) (p>0.05). Intrapulpal thermal changes were shown in Figure 2.

The highest microhardness value was observed in Group 4 (±48.67). Group 2 (±37.09) showed a significantly higher microhardness value than Group 1 (±32.83) (p=0.045). There were no significant differences between Group 3 and Group 4 regarding microhardness values (p>0.05). Group 6 (±28.94) showed a significantly higher microhardness value than Group 5 (±26.92) (p=0.020). Microhardness values were shown in Figure 3.

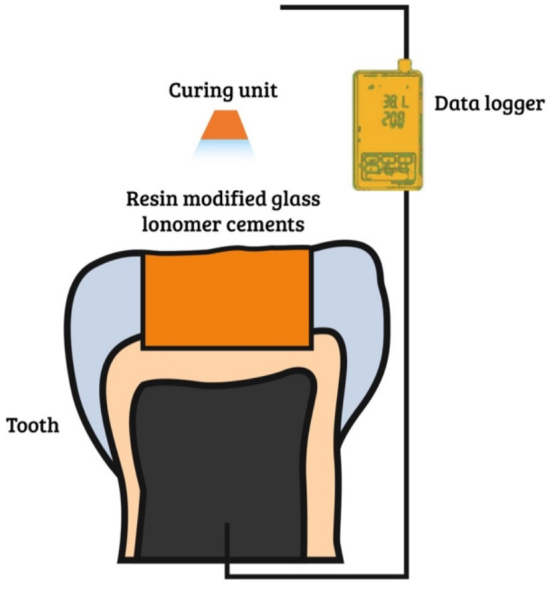

Figure 1. Diagram of measurement of intrapulpal thermal changes

Discussion

The purpose of this study was to compare the microhardness of high viscosity glass ionomer, GC, and BRM polymerized at different polymerization times and evaluated the intrapulpal thermal changes during increased polymerization times. Pulpal temperatures were found significantly different between Groups 1 (±3.29) and 2 (±4.49) and also between Groups 3 (±5.49) and 4 (±6.72). Additionally, microhardness values were found significantly different between Groups 1 and 2, and Groups 5 and 6. The null hypotheses were partially rejected.

Intrapulpal thermal changes can be affected by several factors such as polymerization procedures, cavity preparation procedures, remaining dentin thickness, and type of restorative materials (18). It was reported that increasing the polymerization time can damage the vitality of the pulp tissue (19). It was also reported that increased polymerization time changes the microhardness of the restorative materials (16).

Calorimeter, thermocouple, infrared camera, and differential thermal analysis are techniques to evaluate intapulpal thermal changes (20). However, when the studies were examined, thermocouple device was generally used for the measurements of the intrapulpal thermal changes due to their reliable and sensitive outcomes in temperature changes (21,22).

The tooth pulp is an extensive vascularized tissue (23). Due to this structural property of pulp, intrapulpal temperature increase can be absorbed when the dental tissue is exposed to thermal stimulus (23). Studies reported a high intra-pulpal temperature increase when the pulpal microcirculation model was not used

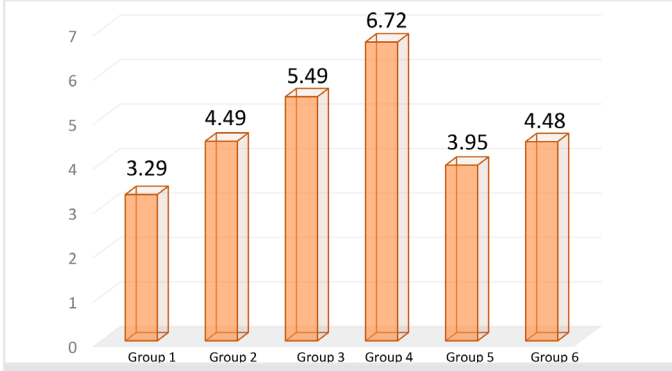

Figure 2. Intrapulpal thermal changes in groups

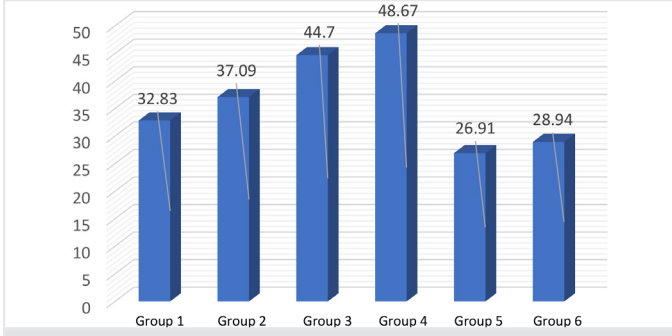

Figure 3. Microhardness values in groups

(24-27). If we had used the microcirculation model, perhaps the intrapulpal thermal changes would have been different or lower than these results.

The thermal changes in the pulp tissue vary according to the thickness of the dentin in the pulp chamber, cavity preparation technique, the type of restorative material, and the light unit used (18, 28-30). Also, the intensity of the light source and polymerization time can affect the temperature changes in the pulp chamber (31,33). In this study, an LED curing unit was used, 1,170 mW/cm^2, 385-515 nm at different times for Equia Fil and BioActiva. In addition, Carboled with 1,400 mW/cm^2 for the polymerization of GC fillings was used. The highest pulp temperature increase was obtained in the 90 sec polymerization in Carboled used group. This may be due to the high output power of the light device and the longer activation time. The higher temperature increase in the Equia Fil group in which the LED was applied for 40 sec compared to the 20 sec may also be due to the prolonged polymerization time. In a study by Altan et al. (30) the temperature increase of Equia Fil and GC was compared and they found the lowest temperature increase in Equia Fil Group and the result of that study was similar to the present study.

The studies showed that the remaining dentin thickness was effective in causing pulp damage by intrapulpal thermal changes (33,34). Aguiar et al. (34) observed an intrapulpal temperature of 5.6 °C for 1 mm remaining dentin, 5.3 °C for 2 mm remaining dentin, and 2.4 °C for 3 mm remaining dentin. Botsali et al. (18) reported that the intrapulpal temperature increase in 1 mm remaining dentin was more than that in 2 mm dentin thickness. Botsali et al. (18) found that both the 1 mm and 2 mm remaining dentin thicknesses for the GC Group showed the highest intrapulpal temperature increase when compared to two different resin-modified GIC cements (34,35). In this study, the highest intrapulpal temperature increase was observed in GC groups at 1 mm dentin thickness.

Surface microhardness is one of the methods used to evaluate the physical strength of materials (36). Brinelll (37) are commonly used in measuring the microhardness value of restorative materials. Vickers test method was used in this study due to the availability of equipment and suitability for all materials and surfaces (38,39). In addition, surface hardness is related to the content and size of the restorative material (14,15).

Heat application is recommended to improve the mechanical properties of GIC (40,41).

When a glass-ionomer based material was heated to a high temperature, the evaporation of the liquid may result in an increase in the powder to liquid ratio, which in turn strengthens the cement (42). This study measured the microhardness by applying heat for different periods to all restorative materials. For all of the restorative materials, surface microhardness was higher in groups exposed to long polymerization time. Therefore, it can be concluded that the prolonged polymerization time may increase the microhardness and improve the mechanical properties of the materials positively.

It is known that the mechanical properties have become better as the particle size of the restorative materials decrease (43). GCs have developed with the application of nanoparticle technology to create an enamel-like structure (44,45). It is known that enamel is the hardest and stiffest tissue in the human body (46). In addition, fluoroapatite and hydroxyapatite are added to the nanoparticle structure to strengthen their mechanical and physical properties. In this study, the highest hardness value was found in the GC group which might be due to its nanoparticle-containing structure which created an enamel-like structure.

Surface coating application is recommended in glass ionomer cements to prevent early moisture contamination and improve surface properties (9,47). According to the manufacturer's instructions, a nanofill resin surface coat was applied to the Equia Fil Group and (48) silicon-based surface coat material was applied to GC Groups (42). Therefore, the higher surface microhardness of Equia Fil and GC compared to BRM Groups could be due to the application of surface coating materials. Besides, higher microhardness values obtained in GC than in Equia Fil Groups may be due to the different content of surface coating materials.

Although BRM is known as a type of RMGIC, it differs from RMGIC with some structural features. BRM has reactive ionomer glass fillers and rubberized resin component (49). Due to the different content of BRM from other glass ionomer cements, the increase in intrapulpal temperature may not be adversely affected.

The lack of intraoral conditions and the pulpal circulation model were the limitations of this in vitro study.

Conclusion

1. Polymerization of the bioactive material for a long time positively affected the microhardness of the material without causing an increase in pulp temperature while negatively affecting the other glass ionomer-based materials causing an increase in pulp temperature.

Increasing the polymerization time of bioactive material can be recommended.

No temperature increase that would cause pathological damage to the pulp was observed in other groups except for the group of GCs polymerized with light for 90 sec.

During application of GC in clinical situations, clinicians should avoid curing for prolonged time.

In the use of GC remaining dentin thickness is recommended to be more than 1 mm to protect pulp from damage.

Ethics

Ethics Committee Approval: Bezmialem Vakıf University Non-invasive Research Ethics Committee (number: E-54022451-050.01.04-7929/date: 20.03.2021).

Informed Consent: *In vitro* study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.B.K., Design: Z.B.K., E.E.D., N.D., Data Collection or Processing: Z.B.K., Analysis or Interpretation: N.D., M.K., Literature Search: Z.B.K., E.E.D., M.K., Writing: Z.B.K., N.D., M.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

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Evaluation of the Relationship Between Delivery Type and Craniofacial Morphology and Condylar Symmetry

Doğum Tipiyle Kraniyofasiyal Morfoloji ve Kondiler Simetri Arasındaki İlişkinin Değerlendirilmesi

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ABSTRACT

Objective: To assess the effects of delivery types on growth patterns and mandibular asymmetry.

Methods: One hundred six patients were divided into two groups as those who were born via normal delivery and via cesarean delivery. Skeletal growth patterns were measured on cephalograms using NemoCeph software (Nemotec, Madrid, Spain). The condylar, ramal and total asymmetry indexes were calculated on panoramic radiographs using the ImageJ software (ImageJ software, 1.37, National Institutes of Health, Bethesda, Maryland, USA). The mothers of the patients were also asked to respond to questions on their childbirth experiences and the infancy stages of their children.

Results: There was no statistically significant difference between the groups in terms of their skeletal, dental and soft tissue parameters on their cephalometric images ($p>0.05$). While there was a significant difference in the asymmetry index scores of the normal delivery group based on their Co-Sg distance values, there was a significant difference in the index scores of the cesarean delivery group based on their Sg-Go distance values ($p<0.05$). No statistically significant difference was observed between the asymmetry index values of the two groups ($p>0.05$). A significant correlation was observed between the gestational weeks of the patients at birth and their total asymmetry scores ($p<0.05$).

Conclusion: Types of delivery did not affect growth patterns significantly. However, more asymmetric condyles were observed in the normal delivery group, and more ramus asymmetries were observed in cesarean delivery group. There was also a relationship between preterm birth and mandibular asymmetry.

Keywords: Normal delivery, cesarean delivery, asymmetry, radiographic analysis

ÖZ

Amaç: Doğum yöntemlerinin büyüme paternleri ve mandibuler asimetri üzerindeki etkilerini değerlendirmektir.

Yöntemler: Yüz altı hasta normal doğum ve sezaryen doğum olarak iki gruba ayrıldı. İskelet büyüme modelleri, NemoCeph yazılımı (Nemotec, Madrid, İspanya) kullanılarak sefalogramlarda ölçüldü. ImageJ yazılımı (ImageJ yazılımı, 1,37, National Institutes of Health, Bethesda, Maryland, ABD) kullanılarak panoramik radyografilerde kondiler, ramal ve toplam asimetri indeksleri hesaplandı. Hastaların annelerinden doğum deneyimlerine ve çocuklarının bebeklik dönemlerine ilişkin soruları da yanıtlamaları istendi.

Bulgular: Gruplar arasında sefalometrik radyograflarda iskelet, diş ve yumuşak doku parametreleri açısından istatistiksel olarak anlamlı fark yoktu ($p>0,05$). Co-Sg mesafesi değerlerine göre normal doğum yapan grubun asimetri indeks puanlarında anlamlı fark bulunurken, sezaryen ile doğum yapan grubun Sg-Go mesafesi değerlerine göre indeks puanlarında anlamlı fark vardı ($p<0,05$). İki grubun asimetri indeks değerleri arasında istatistiksel olarak anlamlı bir fark gözlenmedi ($p>0,05$). Hastaların doğum anındaki gebelik haftaları ile toplam asimetri skorları arasında anlamlı bir korelasyon gözlendi ($p<0,05$).

Sonuç: Doğum şekli büyüme paternlerini önemli ölçüde etkilememiştir. Ancak normal doğum grubunda daha fazla asimetrik kondil, sezaryen doğum grubunda daha fazla ramus asimetrisi gözlendi. Erken doğum ile çene asimetrisi arasında da bir ilişki bulunmuştur.

Anahtar Sözcükler: Normal doğum, sezaryen doğum, asimetri, radyografik analiz

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Introduction

Malocclusions may cause social and health problems at any age (1). Several theories have been proposed on the formation of malocclusions. The most widely agreed upon theory is the functional matrix theory, which argues that bone develops in response to changes in functional matrices (2).

Moss reported that the coronoid process does not develop after the unilateral resection of the temporal muscle because it is dependent on the demands of the functional matrix (temporalis muscle) of the coronoid (skeletal unit) (2).

Face remodeling and growth are also linked to the development of neurocrania. Most of the maturation process of the brain occurs in the first 2 years of life. During this time, deviations in the maturation process may lead to abnormal skeletal patterns. Another theory associated with this condition is the osteopathic theory. The osteopathic theory specifies neuromuscular and joint dynamics for the primary movements of cranial respiration and the formation of surrounding facial structures (3).

In their study that was conducted with the participation of 1,250 children, Frymann (4) observed that osteopathic birth trauma created cranial dynamics that caused complications such as abnormal craniofacial shapes and abnormal neuromotor development in the future. In their study, it was shown that osteopathic disorders of the occipital condyle were observed quite frequently. This is because the 12th cranial nerve, which innervates the lingual muscles, is located in the condylar canal (5). It is assumed that birth trauma may cause orthodontic problems in two ways: the formation of irregular facial structures as a result of cranial growth and changes in sucking-swallowing patterns (4).

There are a few studies investigating the effects of birth trauma on dental malocclusions using the Angle classification. To better understand the links between the osteopathic theory and dental occlusion, Cattaneo et al. (3) reported that precise and more accurate evaluations are necessary. Schoenwetter (6) stated that there might be shape changes in the maxilla since premaxillary compression occurs in normal birth, and they believed that two children born by cesarean section had symmetrical narrow maxillae, and the pressure the fetus was exposed to before birth caused the deformity.

Irma et al. (7) found that birth by cesarean delivery seemed to be slightly protective against the risk of malocclusions.

While some studies have focused on dental occlusions, no studies exist on the cephalometric assessment of skeletal and soft tissue growth models and mandibular asymmetries. The aim of this study was to determine whether type of delivery influenced skeletal and soft tissue growth patterns and mandibular condylar asymmetry status.

Our null hypothesis was that there would be no difference in the asymmetry index between the two methods.

Methods

This study was approved by the Ethics Committee of the Bezmialem Vakıf University (12/2019). Informed consent was received from the patients for their orthodontic treatments.

For the study, 372 patients who were admitted to Bezmialem Vakıf University for orthodontic treatment were selected. The following inclusion and exclusion criteria were considered before the examinations of the radiographic images of patients.

Inclusion criteria: (1) Having been born via spontaneous vaginal delivery or cesarean delivery, (2) having good-quality radiographic records before orthodontic treatment, and (3) being in the 6th cervical vertebral maturation stage.

Exclusion criteria: (1) Having been born via forceps-assisted vaginal delivery, (2) having been born before 32 weeks of gestation, (3) being a cleft lip and palate patient, (4) history of orthognathic surgery, (5) systemic or metabolic diseases, and (6) history of facial trauma.

After applying the inclusion criteria, 108 patients (38 males, 70 females) were included in this study. The patients were divided into two groups as the normal delivery group (36 females, 18 males; mean age: 14.21±2.27 years) and the cesarean delivery group (34 females, 20 males; mean age: 14.16±2.19 years).

The mothers of the patients who were included in the study were asked to respond to questions on their childbirth experiences such as the gestational week of childbirth, duration of labor, the birth order of the child included in the study (first child vs. other), status of breastfeeding in the first 6 months, duration of breastfeeding, use of an infant bottle/pacifier, duration of using an infant bottle/pacifier, and timing and form of introduction to solid food (Table 1).

Cephalometric Analyses

Lateral cephalometric images were taken using the same device (Planmeca ProMax, Helsinki, Finland) and with the same standardized method. All measurements were performed by the same researcher (İ.E.M.) using the NemoCeph program (Nemotec, Madrid, Spain). Skeletal, vertical, dental, and soft tissue measurements were performed in this study. The included measurements are shown in (Figure 1).

Vertical Condylar Symmetry Evaluations

Digital panoramic radiographs (Planmeca Promax Digital Panoramic X-ray Unit, Planmeca Inc, Helsinki, Finland) taken before the orthodontic treatments of the patients were used for the condylar asymmetry measurements. The ImageJ software (ImageJ software, 1.37, National Institutes of Health, Bethesda, Maryland, USA) was used for the measurement of the distance between the Condylion (Co) and Sigmoid Notch (Sg) (condylar height), between the Sg and Gonion (Go) (ramal height), and between the Co and Go (total height) to evaluate condylar asymmetry (Figure 2). The scale settings were calibrated after importing the radiographic images, and the linear distances between the examined points were measured in pixels.

Table 1. Comparison of the mothers' birth experiences between cesarean and normal birth groups

	Normal delivery		Cesarean delivery		
	Mean	SD	Mean	SD	p-value
Week of birth	37.41	2.15	36.57	3.60	0.1
Duration of the labour (hours)	4.8	1.9	-	-	0.1
Solid food time (months)	7.83	4.18	6.83	2.66	0.1
Breastfeeding time (months)	15.07	8.05	13.11	9.16	0.2
Pacifier/bottle time (months)	9.30	9.18	12.69	10.73	0.08
Nutrition for the first 6 months	n	%	n	%	
Breast milk	46.00	85.2%	34.00	0.63	
Formula	4.00	7.4%	10.00	18.5%	
Both	4.00	7.4%	10.00	18.5%	
Type of nutrition					
Bottle	5.00	9.3%	14.00	25.9%	
Breast feeding	44.00	81.5%	32.00	59.3%	
Both	5.00	9.3%	8.00	14.8%	
Which solid food					
Yogurt	12.00	22.2%	17.00	31.5%	
Soup	12.00	22.2%	14.00	25.9%	
Formula	8.00	14.8%	2.00	3.7%	
Fruit puree	32.00	40.7%	21.00	38.9%	
Using of pacifier/bottle					
None	22.00	40.7%	16.00	29.6%	
Pacifier	17.00	31.5%	10.00	18.5%	
Bottle	12.00	22.2%	17.00	31.5%	
Both	3.00	5.6%	11.00	20.4%	
Child order					
First	23.00	42.6%	28.00	51.9%	
Subsequent	31.00	57.4%	26.00	48.1%	

Independent t-test was used, SD: Standard deviation, n: Number of samples

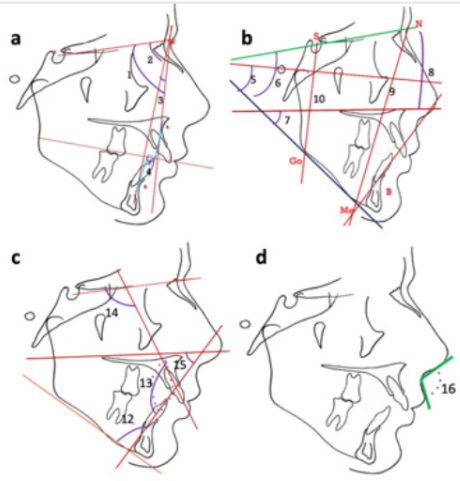

Figure 1. Cephalometric variables, a; 1. SNA°, 2. SNB°, 3. ANB°, 4. Wits appraisal; b; 5. FMA°, 6. MP-SN°, 7. PP-MP°, 8. SN-PP°, 9. Anterior facial height (Na-Memm), 10. Posterior facial height (S-Gomm), 11. Jarabak ratio (ratio of posterior facial height to anterior facial height), c ° 12. IMPA°, 13. interincisal angle (U1-L1°), 14. U1-SN° (long axis of U1 to sella-nasion plane) 15. U1-PP° (long axis of U1 to palatal plane), d; 16. Nasolabial angle

We calculated the asymmetry index with the formula (Asymmetry index = (right-left)/(right + left) x100) used by Lim et al. (8).

Statistical Analysis

The radiographic images of 25 patients were randomly selected after 2 weeks and re-analyzed to assess intra-examiner agreement. The intraclass correlation coefficient (ICC) was used to assess intra-observer reliability. The mean intra-observer ICC was 0.964 (0.932-0.996), which indicated a high level of agreement between the two measurements.

The SPSS package program (version 15.0; SPSS, Chicago, IL) was used for the statistical analyses. The data were tested for normal distribution by using the Shapiro-Wilk test. T-tests and the Mann-Whitney U test were performed to identify differences between groups. Pearson's correlation tests were performed to analyze the relationships between the asymmetry index scores of the patients and their gestational week at birth and feeding and sucking patterns. The level of statistical significance was set at $p<0.05$.

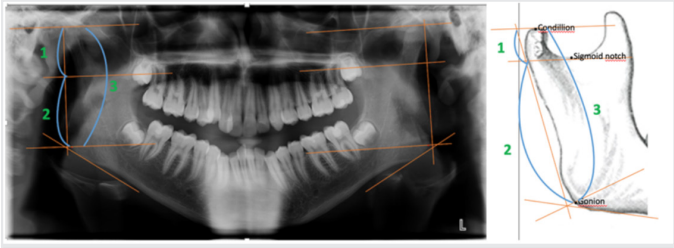

Figure 2. 1; The linear distance between Condyle (Co) and Sigmoid notch (Sg) points, 2; the linear distance between Sigmoid notch (Sg) and Gonion (Go) points, 3; the linear distance between Condilion (Co) and Gonion (Go) points

Results

Table 1 presents the data on the demographic characteristics of the participants. There was no statistically significant difference between the normal delivery and cesarean delivery groups in terms of their demographic characteristics.

There was no statistically significant difference between the normal and cesarean delivery groups in terms of their sagittal, vertical, dental, and soft tissue measurements on cephalometric radiographs (Table 2 and $p>0.05$).

The intra-group comparison in the normal delivery group showed a statistically significant difference in the asymmetry index scores based on the Co-Sg length ($p<0.05$ and Table 3).

The intra-group comparisons in the cesarean delivery group showed a statistically significant difference in the asymmetry index scores based on the Sg-Go length values ($p<0.05$ and Table 3).

Table 2. Comparison of the skeletal, dental and soft tissue cephalometric measurements between groups

	Normal delivery		Cesarean delivery		
	Mean	SD	Mean	SD	P value
SNA°	77.78	4.86	78.22	4.01	0.61
SNB°	74.88	4.56	75.83	4.31	0.27
ANB°	2.88	2.58	2.38	3.48	0.78
NA (mm)	-3.02	3.94	-1.83	4.13	0.13
N-POG (mm)	-9.23	8.47	-6.47	7.33	0.07
Witts(mm)	0.88	3.77	0.16	4.62	0.38
SN-MP°	36.97	8.88	36.57	6.71	0.32
SN°-PP°	9.53	5.01	9.64	4.36	0.42
PP°-MP°	29.53	6.27	28.66	6.46	0.39
U1-SN°	101.41	9.34	99.83	8.16	0.35
U1-PP°	110.31	8.01	107.10	15.65	0.37
U1-NA (mm)	4.55	3.29	3.57	2.82	0.10
U1-NA°	23.64	8.47	21.82	7.56	0.24
IMPA°	90.61	7.17	90.55	6.95	0.96
L1-NB (mm)	4.26	2.31	4.32	2.32	0.89
L1-NB °	23.23	6.52	23.00	6.24	0.85
U1-L1°	130.26	11.67	132.97	10.42	0.41
Nasolabial angle°	113.80	18.32	114.41	15.36	0.84
Upper lip (mm)	-3.65	2.84	-3.56	2.86	0.88
Lower lip (mm)	-1.23	2.59	-1.84	2.96	0.25

Independent t-test was used, SD: Standard deviation

Total asymmetry index indicated a statistically significant difference for both groups (p<0.05 and Table 3).

The inter-group comparisons indicated no statistically significant differences in the asymmetry index scores between the groups based on their Co-Sg, Sg-Go, and Co-Go lengths (p>0.05 and Table 4).

A significant negative correlation was observed between the gestational weeks of the patients at birth and their total asymmetry index scores (p<0.05 and Table 5). On the other hand, no significant correlation was found between the total asymmetry index scores of the patients and other characteristics of them presented in Table 5 (p>0.05).

Discussion

Abnormal muscle tone may restrict the protective effect of the uterus on the head of the fetus during vaginal delivery, and the compression of the head by the pelvic bones of the mother may result in abnormal cranial development (9). Frymann (4) reported that in cases of vaginal delivery, the duration of the labor should be between 6 and 12 hours to consider the delivery as a normal delivery. The author classified longer or shorter vaginal deliveries as non-normal vaginal deliveries (slow and quick deliveries). This categorization was based fundamentally on the duration of labor as evidence of force applied on the cranium of the infant (4). A higher force on the baby's skull in a non-normal delivery causes occipital condylar dysfunction, which negatively affects the function of the XII pair of the cranial nerves (hypoglossal nerves). The hypoglossal nerve functionally facilitates the motor innervation and posture of the tongue (3,4,10), and the function of the tongue affects the development of craniofacial structures, and accordingly, the formation of malocclusions (11). Another concern is the recent significant increase in the number of cesarean deliveries due to the preferences of mothers and healthcare practitioners. The worldwide cesarean section rate is about 15% in general, even reaching 35-45% in some countries, according to the World Health Organization (12-14). The Turkish Society of Obstetrics and Gynecology reported the cesarean section rate as 5.7% in 1988, 21% in 1998, and over 45% in 2010. Turkey is one of the countries with the highest cesarean section rates in the world, at a current rate of 53.2% (15,16).

It has been reported in the literature that there are some advantages and disadvantages of normal or cesarean deliveries

Table 3. Intra-group comparison of asymmetry index in normal and cesarean delivery groups

	Normal delivery			Cesarean delivery		
	Mean	SD	P value	Mean	SD	P value
Right Co-Sg	127.04	36.02	**0.01**	132.26	38.21	NS
Left Co-Sg	120.82	35.72		130.67	40.60	
Right Sg-Go	221.59	67.97	NS	235.96	62.60	**0.03**
Left Sg-Go	218.75	64.88		230.55	62.97	
Right Co-Go	348.60	90.44	**<0.001**	368.40	84.14	**0.02**
Left Co-Go	339.83	87.95		359.77	86.95	

The value of Co-Go represents the total asymmetry index. Wilcoxon signed-rank test was used, SD: Standard deviation, bold font indicates statistical significance

Table 4. Inter-group comparison of asymmetry index

	Normal delivery		Cesarean delivery		
	Mean	SD	Mean	SD	P-value
Co-Sg	6.06	4.67	6.05	5.14	0.95
Sg-Go	3.09	2.72	3.19	2.39	0.47
Co-Go	2.03	1.46	2.81	3.22	0.32

Mann-Whitney U test was used, SD: Standard deviation

Table 5. Correlation between demographic features and asymmetry indexes

	Co-Sg		Sg-Go		Co-Go	
	r	P value	r	P value	r	P value
Week of birth	0.06	0.51	-0.01	0.88	-0.20	**0.03**
Solid food time (months)	-0.10	0.29	0.09	0.34	0.10	0.31
Duration of the labour (hours)	0.10	0.30	0.03	0.79	0.17	0.09
Breastfeeding time (months)	-0.01	0.92	0.10	0.30	-0.06	0.54
Pacifier/bottle time (months)	-0.17	0.08	0.11	0.27	0.15	0.13

Pearson correlation test was used, r: Correlation coefficient, bold font indicates statistical significance

for both the mother and the infant. Although each procedure carries its own risks for systemic condition and malocclusion development, both methods are routinely performed in clinical obstetrics. While genetic factors are highly effective in the development of malocclusions, it is also known that gestational week at birth, parental age, birth order, birth weight, characteristics of pregnancy, and type of delivery also play a critical role in the etiology of malocclusions (2). Therefore, the aim of this study was to compare cephalometric parameters and facial symmetry characteristics between individuals who were born via cesarean delivery and those born via normal delivery.

To eliminate the possible effects of differential jaw growth and occlusal changes from primary to permanent dentition on the results, patients who completed pubertal growth were included in this study (14,17-19). No statistically significant differences in sex and age were observed between the normal delivery and cesarean delivery groups.

Cattaneo et al. (3) and Zhou et al. (20) reported that children born via normal delivery had lower rates of malocclusions than those born via cesarean delivery. On the other hand, Irma et al. (9) reported that cesarean delivery had slightly protective effects against the risk of malocclusion development. In our study, no significant difference was found between the groups in terms of their cephalometric values. Cattaneo et al. (3) defined deliveries lasting 6-12 hours as normal deliveries in their study. On the other hand, Zhou et al. (20) did not define a specified duration of delivery considered natural. This difference in findings may be attributed to the fact that the births of the patients in the normal delivery group took shorter (4.8±1.9 hours) as the mothers of most of these patients were multiparous. Another possible explanation might be that patients with severe skeletal malocclusions requiring orthognathic surgery in which genetic factors were significantly effective were excluded from this study.

We used panoramic radiographs to examine Co-Sg, Sg-Go, Co-Go distances, and asymmetry index values. Many studies have reported that panoramic radiographs give reliable results in the measurement of condylar asymmetry and condylar height (21-23). No statistically significant differences in condylar asymmetry, ramal asymmetry, or total asymmetry index values were found between the groups in this study. On the other hand, we found a statistically significant difference between the right and left sides in terms of condylar height in the normal delivery group, as well as a significant difference in terms of ramus height in the cesarian delivery group. However, a statistically significant difference was observed in total asymmetry index for both groups. Therefore, the null hypothesis was rejected. A relationship between labor and delivery stress and orthodontic malocclusions was reported (3). This was because asymmetric mechanical forces could induce deviations in the craniofacial bones by the accumulation of stress in the mandibular condyles and the inability to tolerate this stress due to the articulation of the condyle with the skull base (3,4,25). Therefore, this condylar asymmetry could be attributed to the maxillofacial trauma caused by muscular and positional push and pull forces applied to the craniofacial structure during vaginal deliveries (24, 25).

The difference in the position of the mandible between normal and cesarean delivery depending on the way the head is delivered, the localization of the forces that the baby is exposed to during two different types of birth, and the difference in the extension and flexion of the head may have led to this finding.

The condylar asymmetry index values of both groups were similar when compared based on the 3% threshold value proposed by Habets et al. (26) However, to the best of our current knowledge, the present study is the first to investigate the relationship between mandibular asymmetry and type of delivery. It is difficult to compare our findings to those of previous studies evaluating condylar asymmetry, as there have been no studies investigating mandibular vertical asymmetry in cases of different type of delivery. Thus, further studies are needed in this field.

Zhou et al. (20) reported that breastfed children had lower risk levels in terms of malocclusion development. In this study, the majority of the patients in both groups had mixed breast and bottle feeding in the first 6 months. Moreover, the groups had similar results in terms of the duration of breastfeeding, the duration of using an infant bottle/pacifier, and the timing and type of introduction to solid food. Prolonged breastfeeding is one of the factors that prevent malocclusions by restricting bottle-feeding and non-nutritive habits (27,28). One of the possible explanations for the absence of a significant difference between the groups in terms of malocclusions may also be the similar feeding habits of the two groups.

Moreover, in this study while no significant correlations were found between the duration of breastfeeding, the duration of using an infant bottle/pacifier, and the timing of introduction to solid food in the groups and their mandibular asymmetry index scores, a significant negative correlation was identified between gestational week at birth and mandibular asymmetry index scores. It has been reported in the literature that the development of malocclusions is associated with preterm birth (15,29).

Pogliani et al. (30) stated that the risk of plagiocephaly was high in preterm children, and accordingly, the possibility of mandibular asymmetry development was high. On the other hand, the specific mechanism that can explain this association remains unclear (15).

Study Limitations

Finally, this study had several limitations. In this study, data were collected using retrospective questionnaires applied to the mothers of the patients who might not be able to remember every detail of their pregnancy and childbirth correctly (recall bias). Individual variations may also make it difficult to determine the relationship between the variables in prenatal and infantile periods and orthodontic malocclusions. Therefore, further prospective controlled studies with larger sample sizes are needed to determine whether perinatal and infantile variables may increase the risk of malocclusions.

Conclusion

Keeping in mind the limitations of this study, it was concluded that;

- Type of delivery had no significant effect on skeletal, dental, and soft tissue cephalometric parameters.

- The patients born via vaginal delivery tended to have a higher prevalence of condylar asymmetry, whereas those born via caesarean section tended to have a higher prevalence of ramal asymmetry.

- A statistically significant relationship was observed between preterm birth and mandibular asymmetry.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Research Ethics Committee of Bezmialem Vakıf University (protocol no: 54022451-050.05.04).

Informed Consent: The informed consent forms were obtained from individuals included.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.E.M., E.D.Ş., Concept: İ.E.M., E.D.Ş., Design: İ.E.M., E.D.Ş., Data Collection or Processing: İ.E.M., E.D.Ş., Analysis or Interpretation: İ.E.M., E.D.Ş., Literature Search: İ.E.M., E.D.Ş., Writing: İ.E.M.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

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How The Pandemic Has Affected Children's Weight and Height?-A Single Center Experience

Pandemi Çocukların Kilo ve Boylarını Nasıl Etkiledi?-Tek Merkezli Çalışma

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ABSTRACT

Objective: The pandemic lockdown has affected the whole world regarding health, social, and economic aspects. This study aimed to detect the pandemic's effect on children's height and weight.

Methods: The study was a retrospective cohort study. The data were collected from patients aged 48 to 144 months who were followed up for three years between 2020 and 2022 in the pediatric outpatient clinic. Height and weight percentiles, and body mass index values of the patients were recorded.

Results: Eighty children were included in the study. It was determined that the children's annual body weight percentile values increased statistically significantly between 2020-2022. It was determined that there was a significant increase in the weight percentile values of children aged 48-59 months in all three years (p values were 0.00, 0.00, and 0.00, respectively). While there was no change in the height percentile value between 2020-21, an increase was observed in other years (2021 vs. 2022 and 2020 vs. 2022). While there was no increase in body weight percentile values between 2020-2021 in children aged 60-95 months, it was observed to increase in the following two years (p values were 0.00, and 0.00 respectively). In children aged 96-144 months, there was no statistically significant increase in weight and height percentile values over the years.

Conclusion: The pandemic caused weight gain and increased the prevalence of obesity in children. While this increase was more

ÖZ

Amaç: Pandemi döneminde uygulanan karantina tüm dünyayı sağlık açısından ve sosyal ve ekonomik açılardan etkilemiştir. Bu çalışma, pandeminin çocukların boy ve kiloları üzerindeki etkisini tespit etmek için planlanmıştır.

Yöntemler: Çalışma, retrospektif bir kohort çalışmasıdır. 2020-2022 yılları arasında, pediyatri polikliniğinde üç yıl boyunca takip edilen 48 ile 144 aylık hastalar çalışmaya dahil edilmiştir. Hastaların boy ve kilo persentilleri ile vücut kitle indeksi değerleri kaydedilmiştir.

Bulgular: Çalışmaya 80 çocuk dahil edilmiştir. Çocukların 2020-2022 yılları arasındaki yıllık vücut ağırlığı persentil değerlerinin yıllara göre istatistiksel olarak anlamlı bir şekilde arttığı belirlendi. Çocukların yaş durumu ile vücut ağırlığı ve boy persentil değerlerinde ise her üç yılda da 48-59 aylık çocukların ağırlık persentil değerlerinde anlamlı bir artış olduğu tespit edildi (p değeri sırasıyla; 0,00, 0,00 ve 0,00). Boy persentil değerinde 2020-2021 yılları arasında bir değişiklik olmazken, 2021 ve 2022 arasında ve 2020 ve 2022 arasında değişiklik gözlendi. Altmış-95 aylık çocuklarda 2020-2021 yılları arasında vücut ağırlığı persentil değerlerinde artış görülmezken, takip eden iki yılda artış gözlendi (p değeri sırasıyla; 0,00 ve 0.00). Doksan altı-144 aylık çocuklarda ise ağırlık ve boy persentil değerlerinde yıllara göre istatistiksel olarak anlamlı bir artış görülmedi.

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ABSTRACT

pronounced in children aged 48-59 months, no weight gain was observed in children aged 96-144.

Keywords: The pandemics, pediatric obesity, preschool child, body mass index

ÖZ

Sonuç: Pandemi çocuklarda kilo alımına neden olmuş ve obezite prevalansını artırmıştır. Bu artış 48-59 aylık çocuklarda daha belirgin iken, 96-144 ay arası çocuklarda kilo artışı gözlenmemiştir.

Anahtar Sözcükler: Pandemi, pediyatrik obezite, okul öncesi çocuk, vücut kitle indeksi

Introduction

The measures taken by countries because of the pandemic have had social, cultural, economic, and health effects worldwide (1). Almost all countries took measures such as travel restrictions, removal of social activities, curfews, and school closures during the pandemic. With the restrictions imposed during the pandemic, children's time at home increased, leading to decreased physical activity, changes in nutrition and sleep patterns, and more time in front of screens (2-4). This situation negatively affected their weight gain (5-7).

Before the pandemic, the prevalence of obesity in children had stagnated in many high-income countries and increased in low and middle-income countries (8). However, with the pandemic, there has been an increase in weight gain among children and adolescents in many countries (9-13). In the early days of the pandemic, while the damage in the health and economic fields was much talked about, the fact that it caused weight gain in children was ignored. However, the increase in obesity in children over time has drawn attention in this direction.

This study aimed to examine the effect of the pandemic on the height and weight of children and the distribution of this increase according to years, genders, and age groups. Also, bringing childhood obesity to the agenda, which always maintains its importance, emphasizes its causes, and offer solutions.

Methods

This study was a retrospective cohort study. The study population consisted of patients aged between 24 and 144 months who were admitted to Batman University Pediatric Department for routine examinations between January 2020 and January 2022. Healthy children attending routine examinations at the pediatric outpatient clinic were included in the study.

The records of the patients were obtained retrospectively by searching the electronic database.

Data Collection

Records were obtained from admissions between January 1st and April 30th, 2020, 2021, and 2022. Data for the same months of the 3 years were recorded for each patient.

The patients lived in the center of Ankara, all in residential compounds and apartments. During routine visits, patients were asked whether they went out and their responses were recorded. Children who stated that they did not go out were included in the study.

Children aged 24-144 months (2-12 years) who were healthy at the time of admission, had no symptoms, and had no chronic disease were included in the study.

Children with active disease at the time of presentation, with chronic disease, taking medication for any reason, with missing data, and having measurements outside ±2 standard deviation scores (SDS) were excluded from the study.

A total of 124 files were reviewed, and 80 children who met the study criteria and had complete data were included. The data showed that the children's height and weight percentile values were obtained using the percentile chart modified by Neyzi et al. (10) for Turkish children. Body mass index (BMI) was calculated by dividing the child's weight in kilograms by the square of the child's height in meters. BMI values between the 5th and 84th percentiles were categorized as normal, between the 85th and 95th percentiles as overweight, and ≥95th percentile as obese based on Centers for Disease Control and Prevention values. SD scores were calculated. For SDS, standard deviation values of -2 and +2 were considered normal.

Measurement Tools

In the hospital where the study was conducted, a Mesitaş MC 210® height meter was used to measure children's heights. During height measurements, shoulders, hips, and feet were measured against the vertical board at the back, and the line between the external auditory canal and the lower edge of the eyeball was parallel to the ground. Weight was measured without shoes, wearing a single t-shirt and pants, using an Omron® scale sensitive to 100 g. The same person performed the measurements.

Approval for the study was obtained from the Batman University Local Ethics Committee on January 4th, 2023 (no: 38). The subjects' medical records were tracked and reviewed through the electronic pediatric patient data registry.

Data Analysis

The Statistical Package for the Social Sciences (SPSS) 23.0 software (SPSS Inc, Chicago, IL) was used for statistical analysis. Frequency, percentage, arithmetic mean, and standard deviation were used as descriptive statistical methods to evaluate the data obtained from the study. The normality of the distribution of body weight, height, and BMI values was evaluated using the

Kolmogorov-Smirnov test. The test significance value was p>0.05 and it wasthat the data showed normal distribution characteristics. The study group's body weight, height, and BMI percentile changes according to the years were evaluated using the paired-sample t-test. P values below 0.05 were considered significant.

The G*Power 3.1.9.2 software package was used to evaluate the sample power after the study. As a result of the study, the effect size (effect size: 0.461) was calculated with the percentile values obtained using BMI, and the power of the study was found as 0.98 at an alpha value of 5%.

Results

The study included 80 children, just over half (58.8%) (n=47) of the children were male, and 70% (n=56) were aged 24-59 months. A total of 57.5% (n=46) of mothers and 50% (n=40) of fathers worked in the private sector. A total of 27.5% of mothers worked away from home during the quarantine period. Fifteen percent of children and 58.7% of mothers were ill during the pandemic. Children received online education between March 24th, 2020, and October 5th, 2021. The demographic findings of the patients are shown in Table 1.

It was found that the percentile values obtained from the annual body weight measurements of the children between 2020-2022 increased statistically significantly between the years (p<0.001, p<0.001, and p<0.001, respectively). There was no statistically significant difference between 2020 and 2021 in terms of height percentiles of the children (p=0.07), but the average percentile values obtained in 2022 increased statistically significantly compared with the other years (p<0.001).

The body weight percentile increased from 52% to 68.3%, and the height percentile increased from 54.6% to 60.9%. BMI-SDS values increased from 0.02 to 0.52. The yearly percentile values and BMI-SDS values are given in Table 2.

There was no significant difference in terms of the girls' body weight percentile values between 2020 and 2021 (p=0.31), but there was a significant increase between 2020-2022 and 2021-2022 (p<0.001 and p<0.001, respectively). The body weight increased in boys significantly in the consecutive years (p<0.001, p<0.001, and p<0.001, respectively).

There was no statistically significant difference in terms of the height percentile values between 2020-2021 in girls (p=0.91), but there was a significant increase in height percentile values between 2020-2022 and 2021-2022 (p<0.001 and p=0.01, respectively). The height percentile values in boys increased

Table 1. Children's descriptive characteristics

Descriptive characteristics (n=80)		n	%
Children's gender	Female	33	41.3
	Male	47	58.8
Children's ages	24-59 months	56	70.0
	60-95 months	12	15.0
	96 months and above	12	15.0
Which school did your child go?	Preschool	46	57.5
	Primary/ secondary school	23	28.7
	Kindergarten	11	13.7
Mother's occupation	Housewife	34	42.5
	Officer	34	42.5
	Private, self-employed	12	15.0
Did the mother work remotely from home during the lockdown period?	Yes	22	27.5
	No	58	72.5
Father's occupation	Private, self-employed	41	51.2
	Officer	38	47.6
	Retired/other	1	1.2
Did the child have Covid-19 during pandemic?	Yes	12	15
	No	68	85
Did the mother have Covid-19 during pandemic?	Yes	47	58.7
	No	33	41.3

Covid-19: Coronavirus disease-19

Table 2. Assessment of body weight, height and BMI of children by years

Children's body weight, height and BMI changes		$\bar{X}$	SD	Test values 2020-2021	2020-2022	2021-2022
Body weight percentile %	2020	54.46	29.12	t=2.855 p=0.00	t=-7.367 p=0.00	t=7.674 p=0.00
	2021	57.48	28.27			
	2022	68.36	25.96			
Height percentile %	2020	54.69	26.54	t=1.835 p=0.07	t=-5.186 p=0.00	t=-4.430 p=0.00
	2021	56.14	25.44			
	2022	60.95	23.32			
BMI-SDS	2020	0.02	0.82	t=-2.153 p=0.03	t=-5.918 p=0.00	t=5.803 p=0.00
	2021	0.13	0.85			
	2022	0.52	0.84			

Independent Sample t-test p<0.05*
BMI: Body mass index, SDS: Standard deviation score

significantly in all 3 years (p=0.01, p<0.001, and p<0.001, respectively).

There was no significant difference in BMI-SDS values between 2020 and 2021 in girls and boys (p=0.06 and p=0.28, respectively), but there was a significant increase between 2020-2022 and 2021-2022 (p<0.001 and p<0.001 for girls and p<0.001 and p<0.001 for boys, respectively). The findings are given in Table 3.

In the evaluation made in the body weight percentile curves with the age status of the children, it was determined that there was a statistically significant increase in all 3 years in children aged 24-59 months (p<0.001, p<0.001, and p<0.001, respectively).

There was no significant difference in body weight percentile values between 2020-2021 in children aged 60-95 months (p=0.05), but a significant increase was found between 2020-2022 and 2021-2022 (p<0.001 and p<0.001, respectively).

In children aged 96-144 months, no statistically significant difference was found between the years (p=0.14, p=0.34, and p=0.95, respectively).

When the height percentile values of the children were analyzed, it was found that there was no statistically significant difference between 2020-2021 in the 24-59-month age range (p=0.06), but there was a significant increase between 2020-2022 and 2021-2022 (p<0.001 and p<0.001, respectively).

A significant difference was found in terms of the height percentile of children aged 60-95 months between 2020 and 2022 (p=0.02), but no significant difference was found between 2020-2021 and 2021-2022 (p=0.17 and p=0.18, respectively).

There was no significant change in terms of the height percentile values of children aged 96-144 months (p=0.96, p=0.63, and p=0.43, respectively).

There was no significant difference in the BMI-SDS change of children aged 24-59 and 60-95 months in 2020-2021 (p=0.07 and p=0.19, respectively). There was a statistically significant increase between 2020-2022 and 2021-2022 (p-values for 24-59 and 60-95 months of age groups were <0.001 and <0.001, respectively).

No statistically significant difference was found in terms of the BMI-SDS change in children of 96-144 months of age according to the years (p=0.96, p=0.63, and p=0.43, respectively).

Body weight, height, and BMI assessments of children by age are given in Table 4.

In 2020 and 2021, all children were between -2 and +2 SDS; in 2022, four children reached +2 SDS. After the pandemic, 5% of 80 children reached the obesity limit. Figure 1 shows how far the BMIs obtained from the children's height and body weight measurements moved away from the standard deviation in their age groups.

Table 3. Body weight, height and BMI assessment of children by gender

Girls (n=33)		$\bar{X}$	SD	Test values		
				2020-2021	2020-2022	2021-2022
Body weight percentile %	2020	58.00	25.94	t=-1.014 p=0.31	t=-4.805 p=**0.00**	t=-5.385 p=**0.00**
	2021	59.87	26.40			
	2022	69.87	25.14			
Height percentile %	2020	61.18	29.29	t=-0.112 p=0.91	t=-2.778 p=**0.00**	t=-2.699 p=**0.01**
	2021	61.33	28.15			
	2022	66.54	26.19			
BMI-SDS	2020	-0.02	0.69	t=-1.907 p=0.06	t=-4.012 p=**0.00**	t=-4.059 p=**0.00**
	2021	0.17	0.75			
	2022	0.55	0.80			
Boys (n=47)		$\bar{X}$	SD	Test values		
				2020-2021	2020-2022	2021-2022
Body weight percentile %	2020	51.97	31.20	t=-3.056 p=**0.00**	t=-5.665 p=**0.00**	t=-5.630 p=**0.00**
	2021	55.81	29.67			
	2022	67.30	26.74			
Height percentile %	2020	55.81	29.67	t=-2.504 p=**0.01**	t=-4.430 p=**0.00**	t=-3.559 p=**0.00**
	2021	67.30	26.74			
	2022	52.50	32.28			
BMI-SDS	2020	0.05	0.91	t=-1.090 p=0.28	t=-4.319 p=**0.00**	t=4.196 p=**0.00**
	2021	0.11	0.92			
	2022	0.50	0.87			

Paired Sample t-test, p<0.05*
BMI: Body mass index, SD: Standard deviation

Table 4. Body weight, height and BMI Assessment of children by age

24-59 months (n=56)		$\bar{X}$	SD	Test values 2020-2021	2020-2022	2021-2022
Body weight percentile %	2020	52.07	28.04	t=-2.749 p=**0.00**	t=-6.986 p=**0.00**	t= -7.213 p=**0.00**
	2021	55.87	27.81			
	2022	67.86	26.12			
Height percentile %	2020	54.46	31.21	t= 1.898 p=0.06	t=4.723 p=**0.00**	t=-3.930 p=**0.00**
	2021	56.46	30.12			
	2022	61.76	28.50			
BMI-SDS	2020	-0.06	0.74	t=-1.844 p=0.07	t=-5.346 p=**0.00**	t=5.404 p=**0.00**
	2021	0.06	0.84			
	2022	0.53	0.83			
60-95 months (n=12)		$\bar{X}$	SD	Test values		
				2020-2021	2020-2022	2021-2022
Body weight percentile %	2020	47.33	32.29	t=-2.120 p=0.05	t=-5.171 p=**0.00**	t=4.279 p=**0.00**
	2021	51.83	30.15			
	2022	68.50	24.50			
Height percentile %	2020	48.33	35.39	t=1.462 p=0.17	t=2.545 p=**0.02**	t=-1.412 p=0.18
	2021	50.25	34.46			
	2022	54.83	33.46			
BMI-SDS	2020	-0.16	0.92	t=-1.394 p=0.19	t=-6.594 p=**0.00**	t=-3.713 p=**0.00**
	2021	-0.00	0.81			
	2022	0.43	0.86			
96-144 months (n=12)		$\bar{X}$	SD	Test values		
				2020-2021	2020-2022	2021-2022
Body weight percentile %	2020	72,75	25,88	t=-1.575 p=0.14	t=992 p=0.34	t=-0.057 p=0.95
	2021	70.66	26.93			
	2022	70.58	28.71			
Height % percentile	2020	62.08	31.25	t=1.106 p=0.29	t=-0.539 p=0.60	t=-1.636 p=0.13
	2021	60.58	31.89			
	2022	63.25	33.46			
BMI-SDS	2020	0.61	0.91	t=0.041 p=0.96	t=0.489 p=0.63	t=0.803 p=0.43
	2021	0.61	0.86			
	2022	0.56	0.90			

Paired Sample t-test, p<0.05*
BMI: Body mass index, SD: Standard deviation

Discussion

The increase in the body weight percentiles of the 80 children in our study throughout the pandemic was statistically significant. Some studies showed that weight gain in children was higher, especially in the younger age group (11-13). One study reported that a 2-month school closure alone in a kindergarten caused a 0.64% increase in obesity (14). Our study found that the increase in the body weight percentile values was higher in children aged 24-59 months (2-5 years) compared with the other age groups, consistent with the literature (13,15-18).

Due to the economic damages caused by the pandemic, families' difficulty in accessing healthy, expensive foods, stocking of foods with long shelf life and high calories, and the ease of access to such foods at home by children may be one of the factors in weight gain (2,7). Children in this age group need support from adults to do physical activity. With the closure of schools and kindergartens, the decrease in their physical activity may affect weight gain in young children. However, we believed that the most important factor was that the psychological stress of mothers caused by the pandemic led them to increase their eating, and they reflected this habit to their children in this age group. Nelson et al. (19) hypothesized that emotions could be transmitted with the same valence within the family. Accordingly, mothers experience this stress by increased eating and passing it on to their children. Studies mention the pandemic's psychological

effects on mothers (20,21). Accordingly, mothers experience this stress by eating more and passing it on to their children.

Another result of our study was that the BMI-SDS value in children aged 96-144 months (8-12 years) showed no statistically significant increase over the 3 years. Children in this age group are more likely to eat unhealthy snacks such as fast food. Difficulty in accessing such foods during quarantine and easier access to healthy home-cooked meals may be a factor in this. In Turkey, children in this age group frequently consume food in school canteens, which mainly sell unhealthy snacks and fast foods. These products are mostly purchased by primary-secondary school students aged 8-14 years (22). School students buy these foods and beverages during lunch breaks and consume them without other alternatives. In some schools, the administration encourages these purchases by placing vending machines in different parts of the school. We thought that the closure of schools during the pandemic and children's difficulty in accessing such foods contributed to this result.

Various studies have examined the relationship between the sex of children and overweight and obesity during the pandemic and reported different results (13-16,23). In the present study, because the increase in BMI-SDS was similar in boys and girls, gender was not identified as a differential variable.

Since the beginning of the pandemic, many studies were published from many countries showing that it caused weight gain in children in their countries (11-15,23-29). The majority of these were cross-sectional studies. In addition, in some studies, weight and height measurements of children were completed with information obtained from families through questionnaires because of difficulties in reaching patients due to the lockdown (13,14,25,29-34).

This study's strength was that the same children's height and weight measurements were followed regularly for 3 consecutive years. Another strength was that these measurements were performed using standardized devices and always by the same healthcare professional.

Study Limitations

Our study had some limitations. Data were obtained from a single center and might not reflect the general population. Also, children's sleep, nutrition, and physical activity status were not asked because it was a retrospective study.

Conclusion

The pandemic has caused weight gain in children and has increased the prevalence of obesity. This increase has been particularly observed in young children. Public health interventions are urgently needed to promote an active lifestyle and physical activity among children and reduce the negative impact of the pandemic on weight gain and childhood obesity. There is also a need to monitor whether this observed weight gain in children will continue and the long-term health consequences. The World Health Organization is also concerned that pandemics will increase in the coming years and that such lockdowns will affect children the most. Relevant institutions have to strategize on future measures to be taken in this regard.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Batman University Local Ethics Committee on January 4th, 2023 (no: 38).

Informed Consent: The subjects' medical records were tracked and reviewed through the electronic pediatric patient data registry.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: N.C.K., T.K.D., Concept: N.C.K., T.K.D., Design: N.C.K., A.S., H.B., H.Ö., Data Collection or Processing: T.K.D., Analysis or Interpretation: A.S., H.B., H.Ö., Literature Search: N.C.K., A.S., H.Ö., Writing: N.C.K., H.Ö.

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Original Article

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In Vitro Investigation of the Effect of Different Mouthwashes Applied to Restorative Dental Materials on Adhesion of *Streptococcus mutans*

Restoratif Dental Materyallere Uygulanan Farklı Ağız Gargaralarının *Streptokokus mutans* Adezyonunda Etkisinin *İn Vitro* Olarak İncelenmesi

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ABSTRACT

Objective: This study aims to evaluate the effect of chlorhexidine gluconate (CHX), Listerine, and boric acid (BA), applied to three different restorative dental materials, on *Streptococcus mutans* (*S. mutans*) adhesion.

Methods: A total of 120 samples were prepared in the study: Composite (Group CR; n=40), glass ionomer cement (Group GIC; n=40) and compomer (Group C; n=40). The upper and lower surface roughness of the samples were measured. After bacterial adhesions, each group was separated into four subgroups (n=10). Three mouthwash and distilled water (DS) were applied for one minute. Subsequently, the remaining *S. mutans* biofilms were examined by colony forming unit count (CFU) and MTT methods. Data were evaluated (p<0.05).

Results: The GIC was the highest, and CR was the lowest in terms of surface roughness. There was a difference among three groups (p<0.001). Log CFU efficiency of bacterial counts of all 3 mouthwashes was higher than distilled water (p<0.001). The effect of all three mouthwash and DW on *S. mutans* log cfu and MTT

ÖZ

Amaç: Bu çalışma, üç farklı restoratif dental materyale uygulanan klorheksidin glukonat (CHX), Listerin ve borik asidin (BA) *Streptococcus mutans* (*S. mutans*) adezyonu üzerindeki etkisini değerlendirmeyi amaçlamaktadır.

Yöntemler: Çalışmada toplam 120 adet numune hazırlandı: Kompozit reçine (Grup CR; n=40), cam iyonomer siman (Grup GIC; n=40) ve kompomer (Grup C; n=40). Numunelerin alt ve üst yüzey pürüzlülükleri ölçüldü. Bakteriyel adezyonlardan sonra her grup dört alt gruba ayrıldı (n=10). Bir dakika boyunca üç gargara ve distile su uygulandı. Ardından, kalan *S. mutans* biyofilmleri koloni oluşturan birim sayısı (CFU) ve MTT yöntemleriyle incelendi. Veriler istatistiksel olarak değerlendirildi (p<0,05).

Bulgular: Yüzey pürüzlülüğü açısından GIC en yüksek, CR en düşüktü. Üç grup arasında fark vardı (p<0,001). Üç gargaranın tümünün bakteri sayımlarının Log CFU etkinliği, distile sudan daha yüksekti (p<0,001). Üç gargara ve distile suyun *S. mutans* log CFU ve MTT değerleri üzerindeki etkisi gruplar arasında farklılık gösterdi (p<0,001). CHX en etkili olanıydı. Restoratif materyal-

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ABSTRACT

values differed between the groups (p<0.001). CHX was the most effective. In terms of restorative material-mouthwash interactions, differences were found between the groups (p<0.05). There was a positive moderate statistically significant correlation between log cfu and MTT values (r=0.636; p<0.001).

Conclusion: BA can be an alternative to other mouthwashes due to its natural structure and the minimal side effects.

Keywords: Bacterial adhesion, restorative dental material, restorative dental treatment, colony forming unit

ÖZ

gargara etkileşimleri açısından gruplar arasında fark bulundu (p<0,05). Log CFU ve MTT değerleri arasında pozitif orta derecede istatistiksel olarak anlamlı bir korelasyon vardı (r=0,636; p<0,001).

Sonuç: BA, doğal yapısı ve yan etkilerinin minimal olması nedeniyle diğer gargaralara alternatif olabilir.

Anahtar Sözcükler: Bakteriyel adezyon, restoratif dental materyal, restoratif dental tedavi, koloni oluşturan birim

Introduction

The aim of restorative dentistry is to regain the natural tooth appearance after correct diagnosis and complete treatment. Many different dental materials have been used to restore teeth (1). These materials have different therapeutic effects (2). In addition, their application in the mouth is closely related to oral hygiene and aesthetics (3). Although finishing and polishing processes remove plaque accumulation and smoothen the surface of the tooth, the adhesion of bacteria cannot be prevented. Dental materials may create a suitable environment for oral microorganisms to adhere to (4).

The bacterial colonization of tissues is one of the most important etiological factors for dental caries, gingivitis, and periodontal diseases. *S. mutans* is the primary microorganism responsible for the formation of dental caries. Therefore, reducing the number of these bacteria in the mouth will greatly contribute to preventing dental caries (5,6).

Brushing and flossing are important for oral hygiene. However, these protective measures are not sufficient to completely destroy bacterial plaque (7). In dentistry, the preventive-therapeutic properties of antimicrobial mouthwashes have been used for many years (8). Therefore, dentists recommend antimicrobial mouthwashes to prevent dental caries and periodontal diseases (9). The level of antimicrobial activity of mouthwashes used today is still not clear.

Chlorhexidine gluconate (CHX) is recognized as the gold standart antimicrobial mouthwash however it has various disadvantages such as pigmentation, taste changes, increased supragingival plaque, and mucosal desquamation (10). Thus it is important to determine alternative mouthwashes compared to CHX in terms of *S. mutans* adhesion.

The aim of this study is to evaluate the effectiveness of various mouthwashes applied to composite resin (CR), compomer (C), and glass ionomer cement (GIC) materials, which are frequently used against *S. mutans*, the primary microorganism responsible for dental caries in the bacterial plaque structure. As a result, comparing the effectiveness of different mouthwashes on different dental materials in reducing *S. mutans* adhesion and colonization and inhibiting plaque metabolism will also be useful in determining the best mouthwash that dentists can recommend to those at high risk of dental caries.

Methods

Specimen Preparation

In this study, three different dental restorative materials were used: GIC (Ketac Molar Easy Mix, 3M Espe, Germany), CR (Tokuyama Estelite® Asteria natural enamel composite, Japan), and C (Dyract® eXtra Compomer, Dentsply, Germany). The properties of the restorative materials and mouthwashes are shown in Table 1.

Using a Teflon ring, 40 disk-shaped specimens (10 mm in diameter x2 mm thick) were prepared from each material. Each material was inserted into the Teflon ring and pressed between the Mylar strips and glass slides to extrude excess material and to produce a smooth surface. The manufacturer's instructions were followed in preparing 120 samples of restorative materials. Specimens were prepared by the same operator (SPT) to eliminate operator-dependent variables. CR and C specimens were polymerized from each surface with a light-curing unit (Elipar S10, 1,200 mW/cm^2, 3M ESPE, St. Paul, MN, USA) in accordance with the instructions for use. The prepared samples were kept at 37 ºC and 100% humidity for 24 hours. Each sample was polished for two minutes using polishing discs (Sof-Lex, 3M ESPE, St. Paul, MN, USA). New polishing discs were used for each sample. The polished samples were subjected to ultrasonic cleaning in DW for 15 minutes.

Surface Roughness Measurement

The surface roughness of the specimens was measured using a profilometer (Marsurf PS 10, Mahr Gmbh, Germany) with a tracing length of 5.6 mm and a cut-off value of 0.8 mm. The profilometer device was recalibrated after the measurement of each sample. Three different measurements were made on the surface of each sample. The average surface roughness value was calculated by averaging the obtained data.

Investigation of Surface Morphology with Scanning Electron Microscope (SEM)

One sample from each group was randomly selected for surface examination. The surfaces of the samples were coated with gold

Table 1. Characteristics of the restorative materials and mouthwashes used in the study

Brand	Type	Chemical composition	Manufacturer
Estelite asteria (NE)	Supra nano-spherical composite Lot W614B	Matrix: Bis-GMA, Bis-MPEPP, TEGDMA, UDMAFiller: Uniform supra-nano spherical silica and zirconia fillers (200 nm). 82 wt %, 71 vol %	Tokuyama Dental, Tokyo, Japan
Dyract XP compomer	Polyacid modified glass ionomer (Compomer) Lot 1910000402	UDMA, TCB resin, TEGDMA, trimethacrylate resin (TMPTMA), dimethacrylate resin, ethyl-4 (dimethylalumino) benzate, BHT, strontium-alumino-sodium-fluoro-phosphorus-silicate glass, strontium fluoride, silicon dioxide, camphorquinone, UV stabilizer	DENTSPLY DeTrey GmbH Konstanz, Germany
Ketac molar easy mix	Glass Ionomer Cement Lot 6383514	Powder: glass fluoro-alumino-silicate, strontium, lanthanum, pigments Liquid: polycarboxylic acid , tartaric acid, water	3M/ESPE GmbH, Seefeld, Germany
Listerin total care	Esansial oils based mouthrinse	Water, ethanol, menthol, eucalyptol, thymol, methyl salicylate, benzoic acid, poloxamer 407, fluoride, zinc chloride, and flavor	Johnson & Johnson USA
Klorhex	Chlorhexidine gluconate based mouthrinse	0.2% chlorhexidine gluconate, glycerin, lemon and peppermint extract esansı	DROGSAN Ankara, Turkey
Boric acid	Boron containing mouthrinse	0.75% boric acid	-

using a coating device (SPI Module Sputter Coater, SPI Supplies, USA). Surface images were recorded using a scanning electron microscope (SEM) (EVO LS10, Zeiss, Oberkochen, Germany) (Figure 1).

Preparation of Artificial Saliva

Dental restorative specimens were sterilized in an autoclave at 121 ºC for 15 minutes before applying bacterial adhesion. Synthetic saliva was applied to sterilized restorative specimens prior to bacterial adhesion to form the pellicle layer. For synthetic saliva, 128 mg NaCl, 16.7 mg $CaCl_2$, 12.5 mg $MgCl_2$ ($6H_2O$), 9.5 mg KCl, 150.75 mg CH_3COOK, 38.6 mg $K3PO_4$ ($3H_2O$) were prepared in one liter of DW, and its pH was adjusted to 7 (11).

Application of Saliva to Samples and Ensuring Bacterial Adhesion

For the bacterial adhesion, an *S. mutans* ATCC 25175 strain obtained from Karadeniz Technical University, Faculty of Medicine, Department of Medical Microbiology was grown in Tryptic Soy Agar (TSA) medium at 37 ºC in 5% CO_2 for 48 hours (12). A single colony was taken from the agar medium and inoculated in a test tube containing 10 mL of TSB medium, and a liquid culture was prepared with a 24-hour incubation. The sterilized samples were placed in 24-well plates after their surface roughness was measured, and 1 mL of the prepared synthetic saliva was added to them and kept at room temperature for 1 hour to form a pellicle. After each sample was washed twice with phosphate buffer and freed from artificial saliva, 1 mL of the liquid bacterial suspension with optical density (OD) 600≅0.5 ($1.5x10^8$ CFU/mL) was added, and the cultures were incubated for 24 hours (11).

The pH Measurements of Mouthwashes

The pH values of the mouthwashes used in the study were measured using a pre-calibrated pH meter (Hanna edge®, USA). For BA, 0.75% concentration was selected according to our previous study (13).

***S. mutans* Adhesion Analysis**

At the end of the incubation period, the samples of which bacterial adhesion was complete were removed from the previous plates and placed in new 24-well plates. One milliliter of the mouthwashes used in the study (Table 1) was added to the samples and left for one minute. After removing the mouthwashes, each sample was transferred to Falcon tubes containing 3 mL of TSB and 0.5 mm glass beads (Sigma-Glass Beads, Germany). The solution in the tubes was vortexed at 1,200 revolutions per minute (rpm) for 5 minutes in a vortex device (Isolab, Laborgerate GmbH, Germany), allowing bacteria to pass into the medium. From the suspension containing the bacteria, dilutions with TSB from 10^{-1} to 10^{-5} were prepared. Cultures were incubated at 37 ºC for 48 hours by seeding 0.1 mL of smear on TSA agar plates from the prepared dilutions. The formed colonies were counted, and the number of colonies per milliliter was determined as a CFU.

Bacteria Viability Analysis

The MTT is a method of expressing cell survival and growth. This method is based on the measurement of metabolically active bacteria metabolizing the yellow tetrazolium salt of

3-(4.5-dimethyl-thiazol-2-yl)-2.5-diphenyltetrazolium bromide (MTT) and forming purple formazan molecules inside the cells (14). Ninety µL of the bacterial suspension released in TSB from the vortexed samples were taken and transferred to 96-well ELISA plates. After adding 10 µL of MTT solution (5 mg/mL MTT in Phosphate Buffered Saline (PBS) and 10 µL of glucose (20%) (15), it was incubated for four hours at 37 ºC in an oven containing 5% CO_2. To dissolve the formazan crystals, 110 µL of dimethyl sulfoxide was added to the bacterial

suspension and incubated for 60 minutes, stirring at 60 rpm at room temperature. Absorbance values were measured at 595 nm with a microplate reader.

Imaging with a Confocal Laser Scanning Microscope (CLSM)

Five hundred µL of overnight liquid culture of *S. mutans* was transferred to microcentrifuge tubes, and the cells were centrifuged at 12,000 rpm for one minute. The precipitated bacteria were suspended in 200 µL of PBS. Cell suspensions prepared in three sets were treated with CHX (Klorhex, Drogsan, Ankara), essential oil-containing mouthwash (Listerine, Johnson & Johnson, USA), and BA for one minute. The mouthwash solutions were centrifuged after the cells had settled, and the treated cells were stained for 15 minutes under light protection using the LIVE/DEAD® BacLight™ Bacterial Viability and Enumeration Kit (Invitrogen, Carlsbad, California, USA). Stained bacteria were observed on a CLSM (Leica DMI8, Leica Microsystems, Germany) with 63x magnification optical lenses using wavelengths of 488 and 532 nm (Figure 2).

Statistical Analysis

Data were analyzed with IBM SPSS V23. The conformity to the normal distribution was evaluated using the Shapiro-Wilk test. Two-way analysis of variance method was used to examine group and solution main effects and interactions on roughness and Log CFU and MTT values. Bonferroni correction was used for multiple comparisons. The Spearman Rho correlation coefficient was used to analyze the relationship between variables. The results were presented as mean and standard deviation for quantitative data. The significance level was taken as $p<0.05$.

Results

Surface Roughness Values

Statistically significant differences were found between the surface roughness values of the materials (Table 2). The average of the surface roughness values of the CR group was the lowest (0.0853 µm), the average surface roughness values of the C group were moderate (0.1405 µm), and the average surface roughness values of the GIC group were the highest (0.4359 µm) ($p<0.001$).

The Examination of Surface Morphology by SEM

SEM images of 2 different magnifications of each of the 3 dental restorative materials are shown in Figure 1.

The pH Values of Mouthwashes

The pH values of the mouthwashes used in the study were measured as 5.8 for CHX, 4.3 for Listerine, and 4.8 for BA, respectively.

S. mutans Adhesion Analysis

In order to determine the adhesion of *S. mutans*, a liquid bacterial culture was added to the surfaces of the test samples. At the end of the 24-hour incubation period, mouthwashes were applied. The number of CFU of the bacteria remaining on the surface of the samples was expressed in CFU/mL. After the mouthwashes were

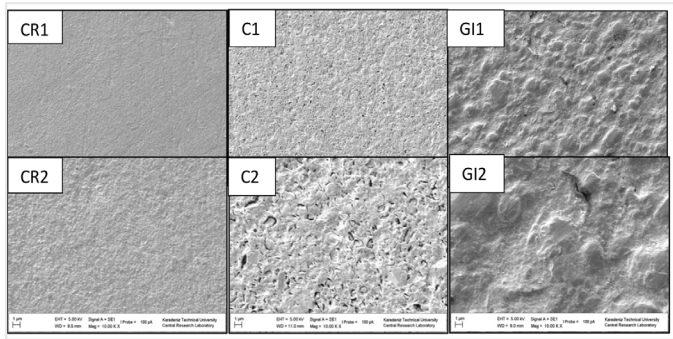

Figure 1. 1 and 2 are 3.00Kx and 10.00Kx magnifications of the SEM images of the groups, respectively

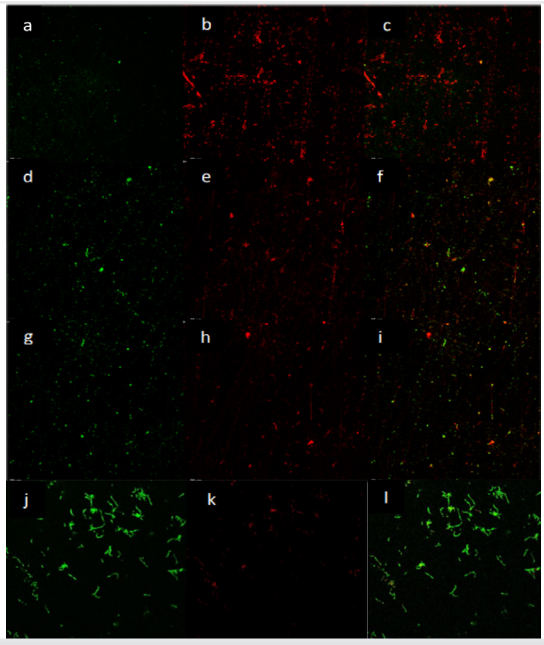

Figure 2. Confocal microscopic analysis of live and dead bacteria after mouthwash applications. (a) CLSM image of viable bacteria after application of CHX. (b) CLSM image of dead bacteria after application of CHX. (c) CLSM image of live and dead bacteria after application of CHX. (d) CLSM image of viable bacteria after application of Listerine. (e) CLSM image of dead bacteria after application of listerine. (f) CLSM image of live and dead bacteria after application of Listerine. (g) CLSM image of viable bacteria after application of BA. (h) CLSM image of dead bacteria after application of BA (i) CLSM image of live and dead bacteria after application of BA. (j) CLSM image of viable bacteria after application of distilled water. (k) CLSM image of dead bacteria after application of distilled water. (l) CLSM image of live and dead bacteria after application of distilled water

CLSM: Confocal laser scanning microscopy, CHX: Chlorhexidine gluconate, BA: Boric acid

Table 2. Comparison of average roughness values in terms of restorative materials

	Composite	Compomer	Glass ionomer cement
	0.0853±0.0203[a]	0.1405±0.0252[b]	0.4359±0.0740[c]

[a-c]There is no difference between groups with the same letter

applied to the restorative materials, the logarithmic calculation of the bacterial counts was made. The logarithmic mean values are shown in Figure 3.

Regardless of the materials, the effect of mouthwash types on CFU was statistically significant (p<0.001). CFU values were statistically significant (p<0.001) according to the restorative material and mouthwash interactions.

Regardless of the restorative material difference, the highest logarithmic value for bacterial adhesion was 6.04 for DW, while the lowest logarithmic value was 4.68 for CHX. The logarithmic values of 4.9 for Listerine and 5.04 for BA showed similar results (Table 3). No significant difference was found between the mean log CFU values obtained from the interactions of GIC-essential oil-containing mouthwash, CIC-CHX, and C-CHX. In particular, the average log CFU value (4.58) in the C-CHX interaction was found to be lower than the others. Other multiple comparison results are presented in Table 3.

No statistically significant correlation was found between the roughness values of the materials and log CFU (r=-0.153; p=0.095) (Figure 4). In the statistical analysis, the lowest surface roughness was on the surface of the CR group (0.0853 µm),

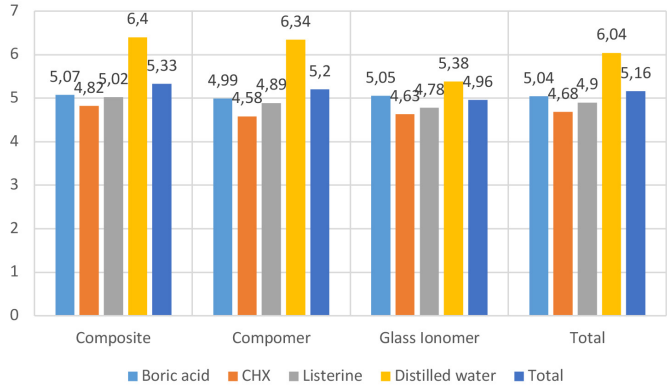

Figure 3. Logarithmic mean values of the number of *S. mutans* attached to the experimental groups

Table 3. CFU values by groups and moutwashes

	Composite	Compomer	Glass ionomer cement	Total
Chlorhexidine	4.82±0.20^{CDEF}	4.58±0.17^{F}	4.63±0.14^{EF}	4.68±0.20^{b}
Listerine	5.02±0.18^{CD}	4.89±0.19C^{DE}	4.78±0.11D^{EF}	4.90±0.19^{c}
Boric acid	5.07±0.21^{C}	4.99±0.22^{CD}	5.05±0.21^{C}	5.04±0.21^{a}
Distilled water	6.40±0.18^{A}	6.34±0.14^{A}	5.38±0.07^{B}	6.04±0.49^{d}
Total	5.33±0.66^{a}	5.20±0.71^{b}	4.96±0.32^{c}	5.16±0.60

$^{a-d}$There is no difference between material/mouthwash types in groups with the same letter, $^{A-F}$There is no difference between interactions between materials with the same letter and mouthwash type, CFU: Colony forming unit count

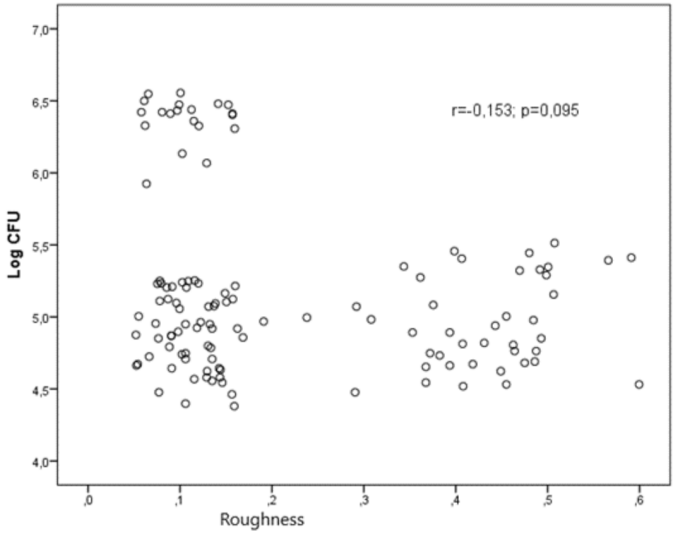

Figure 4. The surface roughness of materials and bacterial adhesions after mouthwashes application to the materials

and the average of *S. mutans* adhesion was determined as the highest. The highest surface roughness was in the GIC group (0.4359 µm), and the average amount of *S. mutans* adhesion was determined as the lowest. No statistically significant correlation was found between surface roughness and *S. mutans* adhesion (p>0.05).

Bacteria Viability Analysis

Regardless of the materials, the effect of the mouthwashes was found to have a statistically significant effect on the MTT values (p<0.001). The mean MTT of DW was 0.296, the mean of the CHX was 0.209, the mean of Listerine was 0.238, and the mean of BA was 0.254 (Table 4). A statistically significant impact was found on the MTT values of the group and mouthwash interaction (p=0.009). The highest average value was obtained in DW (0.353) of the CR group, while the lowest average value was obtained in the CHX (0.185) of the GIC group (Table 4).

Discussion

Adhesion of cariogenic bacteria and biofilm formation are among the most important causes of dental caries (16,17). Although many studies have been conducted on bacterial adhesion on various restorative dental materials (18-23), there is no study with similar experimental design in the literature investigating the effect of mouthwashes applied to these materials on *S. mutans* adhesion.

There is a known significant relationship between the surface roughness of restorative materials and bacterial adhesion (22,24). Bollen et al. (25) stated the critical surface roughness (Ra) value of dental materials for bacterial colonization as 0.2 µm. In another study, the area occupied by the adherent bacteria was found to strongly correlate with the surface roughness of 0.2-0.8 µm Ra (26). Park et al. (27) reported that streptococcal adhesion decreased at a Ra roughness value of approximately 0.15 µm. Considering the relationship between bacterial adhesion and surface roughness in the present study, the roughness values of CR and C were lower than the critical surface roughness value of 0.2 µm, while the roughness value of GIC was higher than this level (p<0.001). SEM images also confirm these findings (Figure 1). In studies dealing with the roughness of restorative dental materials, in parallel with the present study, GIC showed greater surface roughness (28,29). The CR used in this study, on the other hand, had a very low roughness since it had nanofill particles. In the present study, no statistically significant correlation was found between the roughness of the restorative materials and the adhesion of *S. mutans* (Figure 4). This may be due to the detection of *S. mutans* adhesion after applying mouthwashes on restorative dental materials.

The composition of dental restorative materials is another factor that affects the adhesion of *S. mutans* (30). In a study, *S. mutans* adhesion on dental restorative materials was investigated without mouthwash, and it was stated that fluoride release in the materials reduced *S. mutans* adhesion, especially in the early stages of biofilm formation (31). In another study (32), it was reported that conventional GIC inhibited the growth of streptococci with fluoride release. Bis-GMA monomer is often found in the structure of resin-based dental products (33), while TEGDMA monomer is used as a diluent (34). It was reported that the presence of Bis-GMA and TEGDMA products in CR and C materials increased the proliferation of *S. mutans* (35).

In this study, *S. mutans* adhesion (Log CFU =5.38) on the GIC treated with DW according to the colony count method was found to be statistically significantly less than CR (Log CFU =6.40) and C (Log CFU =6.34) materials applied with DW (Table 3). In the MTT method, a statistically different decrease was observed in terms of *S. mutans* adhesion in GIC treated with DW (Table 4). In the light of this information, it is thought that the presence of more fluoride in the structure of the GIC and the presence of Bis-GMA and TEGDMA in the structure of CR and C materials will affect the statistically low *S. mutans* adhesion on the GIC.

Pathogenic bacteria in the oral biofilm are the main factors of periodontal diseases and dental caries. Effective oral hygiene can be achieved by eliminating pathogenic bacteria using mouthwashes (36). In our study, three different mouthwashes were applied to eliminate *S. mutans*, which showed adhesion to dental materials used for restorative purposes. These three mouthwashes showed a statistically significant difference compared to the negative control group, which used DW. Since 0.2% CHX was frequently used in oral antiseptic treatment (37), this concentration of CHX was also preferred in the present study. There is no comparable study reporting the effectiveness of 0.2% concentration of CHX against *S. mutans*, which adheres to CR, C, and GIC in vitro. In clinical studies (38-41), on the other hand, CHX was shown to be the most effective in terms of reducing salivary *S. mutans* and plaque scores. In this study, CHX was the most effective in reducing *S. mutans* adhesion on all restorative materials analyzed by both methods (Table 3 and 4). This may be due to the bactericidal effect of CHX (42).

Table 4. MTT values by groups and mouthwashes

	Composite	Compomer	Glass ionomer cement	Total
Chlorhexidine	0.2382 ± 0.0448^{BC}	0.2045 ± 0.0102^{AC}	0.1854 ± 0.0216^{A}	0.2094 ± 0.0359^{b}
Listerine	0.2921 ± 0.0094^{E}	0.2171 ± 0.0268^{AB}	0.2057 ± 0.0095^{AC}	0.2383 ± 0.0424^{a}
Boric acid	0.3143 ± 0.0384^{E}	0.2276 ± 0.0206^{BC}	0.2206 ± 0.0135^{AB}	0.2542 ± 0.0503^{a}
Distilled water	0.3534 ± 0.0295^{F}	0.2817 ± 0.0267^{DE}	0.2536 ± 0.0319^{BD}	0.2962 ± 0.0513^{c}
Total	0.2995 ± 0.0305^{a}	0.2327 ± 0.0210^{b}	0.2163 ± 0.0191^{c}	0.2495 ± 0.0449

$^{a-c}$No difference between groups with the same letter, $^{A-F}$No statistically significant difference between interactions with the same letter

However, after long-term use of this mouthwash, side effects such as pigmentation, taste changes, increased supragingival plaque, and mucosal desquamation can be seen on teeth and restorations. Therefore, long-term use is not recommended (43). The orientation toward alternative substances with reduced side effects for biofilm control is an important measure.

This study evaluated the effectiveness of essential oil-containing Listerine and BA against *S. mutans* as an alternative to CHX. It has been reported that Listerine is highly effective against the biofilm formed by *S. mutans*. The reason for this is attributed to the antibacterial mint, thyme, and eucalyptus it contains (44). Fine et al. (45) concluded that daily use of essential oil-containing mouthwash would be beneficial in addition to mechanical oral hygiene since it significantly reduced the level of *S. mutans*. Bugno et al. (46) stated that individuals in the group treated with essential oil-containing mouthwashes had lower bacterial counts than those treated with saline solution, and the antimicrobial activity of mouthwash containing essential oil was better than that of 0.12% CHX. According to the data obtained in our study, although the effect of a mouthwash containing an essential oil was statistically significantly higher than DW, it was less than CHX. At the intersection of both methods, Listerine and CHX showed similar activity on GIC when compared. In this case, in individuals with high caries risk, after restoration using GIC, their treatment may be continued with Listerine due to the side effects of CHX. However, some side effects of Listerine are also stated. Zamora-Perez et al. (47) stated that after 30 days of using Listerine containing ethanol, there might be nuclear anomalies associated with DNA damage. It was stated that phenolic compounds in Listerine might cause cell damage to a certain extent. While oral bacteria convert ethanol to acetaldehyde, they also metabolize nicotine to nitrosamine in smokers. The absorption of these products may increase further with phenolic compounds and may have a carcinogenic effect (48).

Boric acid is used in many areas of dentistry. It has been suggested that BA may reduce some clinical measures such as bleeding on probing and alveolar bone loss in treatments performed within the scope of periodontology (49). While it was stated that 6% BA concentration for root canal disinfection was as effective as NaOCl against *Enterococcus faecalis* biofilms (50), it was emphasized that BA at 0.75% concentration could be used in addition to root surface smoothing in the treatment of chronic periodontitis (51). The concentration of BA used in this study was 0.75%. Boron regulates human hormonal metabolism, is an antioxidant, contributes to bone development, strengthens the immune system, accelerates wound healing, reduces the risk of cancer and weight gain, increases mental performance, and cures anemia (52). For these reasons, and due to the side effects of mouthwashes containing CHX and essential oil, BA can be recommended as a natural treatment alternative in cases where it has similar efficacy to these mouthwashes against *S. mutans* adhesion on restorative materials (Table 3 and 4). BA also has anti-inflammatory and antioxidant property (53).

Bacteria were evaluated in experimental samples by plate essay, OD measurement, or a cell cytometer. Plate essay is the most widely used among these methods (54). Although it is inexpensive and widely available, this technique has some disadvantages. These are the large number of Petri plates on which the smear is spread, the need for a large amount of laboratory space for the incubation period, the long incubation time required for colonies to grow, and the manual analysis of each Petri plate one by one (54). MTT, a tetrazolium salt, is a substance that is actively absorbed into cells and is reduced to colored, water-insoluble formazan by a mitochondrial-dependent reaction (14). The MTT-reducing property of cells is taken as a measure of cell viability. Also, the dye density obtained from MTT analysis correlates with the number of viable cells (14). The results found in both colony counting and MTT methods show a positive and moderate significant relationship, as is the case with the correlation graph (Figure 5). However, although the MTT test method is beneficial for the researchers in terms of time, the existing gaps in the knowledge of the application of MTT in bacterial protocols make both methods to be used together in the experiments.

There are some limitations of the present study. Since it was an *in vitro* study, the conditions in the mouth could not be

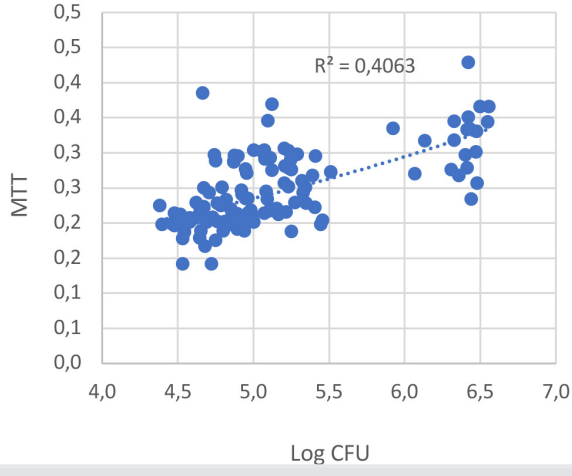

Figure 5. Scatter plot showing the relationship between logCFU and MTT

fully imitated. The effectiveness of mouthwashes on a single bacterium, *S. mutans*, was studied. Individual differences, such as salivary characteristics and nutritional habits, were not considered. In addition, the aging process was not applied to dental materials. The mouthwashes were applied only once. In the future, *in vitro* and *in vivo* studies with different experimental designs examining the effect of BA on other bacteria associated with dental caries are recommended.

Ethics

Ethics Committee Approval: It is an *in vitro* study and an ethics committee certificate is not required.

Informed Consent: *In vitro* study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Consept: S.P.T., K.D., Design: S.P.T., K.D., İ.D., A.O.K., I.B., Data Collection or Processing: S.P.T., İ.D., A.O.K., Analysis or Interpretation: S.P.T., K.D., E.B., S.H., Ü.U., Literature search: S.P.T., Writing: S.P.T., K.D., A.O.K., E.B., S.H.

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Original Article

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Chemical Composition and *In Vitro* Cytotoxicity of Endemic *Thymus brachychilus* Jalas Against Human Breast Adenocarcinoma (MCF-7, HTB-22), Human Lung Adenocarcinoma (A549, CRM-CCL-185), and Human Glioblastoma Cells (U-118 MG, HTB-15)

Endemik *Thymus brachychilus* Jalas'ın Kimyasal Bileşimi ve İnsan Meme Adenokarsinomu (MCF-7, HTB-22), İnsan Akciğer Adenokarsinomu (A549, CRM-CCL-185), İnsan Glioblastoma Hücrelerine (U-118 MG, HTB-15) *İn Vitro* Sitotoksisitesi

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ABSTRACT

Objective: *Thymus* have 341 species in the world and 46 species in Türkiye, 19 of them are endemic. *Thymus* species are used for stomachache, cold, shortness of breath, cough, bronchitis, diabetes in Aladağlar (Niğde). In this study, essential oil (EO) analysis of *Thymus brachychilus*, liquid chromatography/mass spectrometry (LC/MS) analysis of ethanol extract, and its effects on the cell lines mentioned in the title were investigated for the first time.

Methods: The endemic *Thymus brachychilus* Jalas was collected from Aladağlar Mountains, from 3,290 meters. Voucher specimens were prepared after the plant species were identified and kept at the herbarium (HERA 1029). 100 g of dried and powdered aerial part of the plant material was distilled for three hours, yielding 0.42 mL of volatile oil using a Clevenger-style apparatus. The 3.28 g ethanol extract was obtained from 100 g plant. An Agilent GC-FID/MS

ÖZ

Amaç: *Thymus*'un dünyada 341, Türkiye'de 46 türü bulunmakta olup bunlardan 19'u endemiktir. Aladağlar'da (Niğde) *Thymus* türleri mide ağrısı, soğuk algınlığı, nefes darlığı, öksürük, bronşit, şeker hastalığında kullanılmaktadır. Bu çalışma ile, *Thymus brachychilus*'un uçucu yağ analizi, etanol ekstraktının (EE) LC/MS analizi ve bu hücre hatları üzerindeki etkileri ilk kez araştırıldı.

Yöntemler: Aladağlar'ın 3.290 metre yüksekliğinden toplanan endemik *Thymus brachychilus* Jalas'ın tür tayini yapıldıktan sonra ve herbaryum örneği haline getirilip, herbaryum numarası verilerek (HERA 1029) saklanmaktadır. 100 g kurutulmuş ve toz haline getirilmiş toprak üstü kısımlardan oluşan bitki materyali, Clevenger aparatı kullanılarak 3 saat süreyle distile edildi ve 0,42 mL uçucu yağ elde edildi. Yüz g bitkiden 3,28 g etanol ekstresi elde edildi. Uçucu yağ numunelerini analiz etmek için bir Agilent GC-FID/MS sistemi

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ABSTRACT

system was used to analyze EO samples. Phenolic compounds of the extract were analyzed using LC-HRMS. MTT assay was used to evaluate the cytotoxicity of EO and ethanol extract.

Results: Thymol (48.11%), *p*-cymene (12.92%), carvacrol (11.14%) were the major components of the EO. For the extract, the IC50 values were calculated to be between 1.64-15.76 µg/mL, while the values of IC50 were calculated between 68.94-101.2 µg/mL for the essential oil.

Conclusion: Both the ethanol extract and the EO caused cell death in the tested cell lines. However, the extract appeared to be more effective compared to the essential oil. Besides that, a difference between the cell types could be seen, where the U118 MG neuronal cells appeared to be the most sensitive cell line.

Keywords: *Thymus brachychilus*, Aladağlar, essential oil, thymol, GC-MS, cytotoxic activity

ÖZ

kullanıldı. Ekstrenin fenolik bileşikleri, LC-HRMS kullanılarak analiz edildi. Uçucu yağ ve etanol ekstrelerinin sitotoksisitesini değerlendirmek için MTT testi kullanıldı.

Bulgular: Thymol (%48,11), p-cymene (%12,92), carvacrol (%11,14) uçucu yağın ana bileşenleriydi. Ekstre için IC50 değerleri 1,64-15,76 µg/mL arasında hesaplandı. Uçucu yağ için ise IC50 değerleri 68,94-101,2 µg/mL arasında hesaplandı.

Sonuç: Hem EE, hem de uçucu yağ test edilen hücre hatlarında hücre ölümüne neden oldu. Bununla birlikte, ekstrenin uçucu yağa kıyasla daha etkili olduğu görüldü. Bunun yanı sıra, hücre tipleri arasında da bir fark görüldü, U118 MG nöronal hücreleri en hassas hücre hattı olarak tespit edildi.

Anahtar Sözcükler: *Thymus brachychilus*, Aladağlar, uçucu yağ, timol, GC-MS, sitotoksik aktivite

Introduction

Thymus is a member of Lamiaceae family. It has 341 species in the world (1), 46 species in Turkey, and 19 of them are endemic (2,3). The *Thymus* genus generally has small shrubs, cushion plants, and perennial herbs. *Thymus brachychilus* Jalas is an endemic taxon of the Irano-Turanian phytogeographical region. The upper lip of the calyx is shorter than the lower teeth. Bracts resemble leaves and are 0.8 to 1.5 mm broad, narrowly rhombic, progressively thin into a short petiole. Leaves are narrower, 0.4-0.8 mm wide, and have patent coarse hairs on the stems and leaves. The oil spots are mainly orange to red. Flowering time is between 6th and 8th months. It grows in screes and rocks, 1,800-3,660 meters. *Thymus leucotrichus* Hal. and *Thymus serpylloides* Bory are the closest relatives (3). The common name of *Thymus brachychilus* around Niğde is "Mor kekik" (4). *Thymus* species are used internally in the form of tea prepared as an infusion for stomachache, cold, shortness of breath, cough, bronchitis, diabetes among the people in the villages around Niğde/Aladağlar (5). In a study conducted to determine the plants visited by honeybees in Mersin, beekeepers selected according to the data obtained from Mersin Beekeepers Association and determined criteria were interviewed, and visits were made to the areas where beekeepers regularly put their hives. *Thymus brachychilus* species have been identified among the plants most visited by bees to collect nectar (6). It is used in the production of a special cheese in Erzincan (7). One of the morphological closest species *Thymus leucotrichus* Hal. subsp. *leucotrichus* Hal. Is used for colds, flu, high cholesterol in Giresun (8). Species most similar to *Thymus brachychilus* in terms of chemical content are *Thymus kotschyanus* Boiss. & Hohen. and *Thymus praecox* Opiz in Türkiye. *Thymus kotschyanus* infusion is used as a sedative in Bingöl (9), for abdominal ailments, backache, cancer, colds, diabetes, enteralgia, hypertension, and as anthelmintic in Iğdır (10), for colds in Bingöl and Kahramanmaraş (9,11), for gastritis and to treat shortness of breath in Hakkari (12), to lower high cholesterol in Elazığ (13). *Thymus praecox* is used for the treatment of diabetes (Amasya) (14). The essential oil of *Thymus brachychilus* was first identified in the current study.

Methods

Plant Material

Thymus brachychilus samples were collected from the Maden and Cimbar Valleys in the Aladağlar mountain range, also known as Anti-Taurus Mountains (Niğde-Turkey). The location of the plant was rocky and at the altitude of 3,290 meters. Voucher specimens were prepared after the plant species were identified by authors. The Altınbaş University Pharmacy's Faculty's herbarium housed these voucher specimens (HERA 1029).

Thymus brachychilus Essential Oil Isolation

100 g of dried and powdered plant material was distilled for three hours using a Clevenger apparatus. The essential oils were dried over anhydrous sodium sulfate, and then stored at a temperature of 4 ºC until use.

Extraction of Plant Materials

The aerial parts of *Thymus brachychilus* were air-dried at room temperature in the shade, and then ground into powder. *Thymus brachychilus* powder was macerated with a ratio of 1 part of plant soaked in 10 parts of solvent, by using 96% ethanol solvent, in a tightly closed container for 3 days, and protected from light, while stirring frequently. The solvent was evaporated to dryness under rotary evaporator (Heidolph Hei-VAP Advantage Rotary Evaporator) at a temperature of 40 ºC with a speed of 120 rpm and 3.28 g extract was obtained from 100 g plant.

Analysis of Essential Oil

Essential oil (EO) samples were examined using an Agilent GC-FID/MS system (Santa Clara, California, USA). It included an Agilent 7890B GC-FID and an Agilent 5977E MS detector connected by a capillary column splitter. With the use of an

Agilent G4513A auto injector, 1 µL of sample EO solutions in 10%, v/v, *n*-hexane were injected. The temperature program for the HP-5MS column (30 m, 0.25 mm, 0.25 µm) was as follows: 60 ºC isothermal for 5 minutes, then elevated to 180 ºC at a rate of 3 ºC/min. Further, temperature was kept 5 minutes isothermally. Helium was used as a carrier gas at a constant flow rate of 1.5 mL/min. A split ratio of 1:50 was chosen. The temperatures of the injector port, MSD transfer line, ion source, quadrupole, and FID, among other system components, were maintained at 250 ºC, 250 ºC, 230 ºC, 150 ºC, and 220 ºC, respectively. The FID dry air and H_2 flow were adjusted to 400 mL/min and 30 mL/min, respectively. Mass spectra between 45 and 450 m/z were captured.

Identification of the compounds was done by co-injecting reference substances and comparing the spectrum data of the compounds to the NIST 11 Mass Spectral Library (NIST11/2011/EPA/NIH). Retention indices were computed using C7-C40 homologous alkane series and then compared to data from the NIST online webbook. Using an external standard method and calibration curves obtained from GC-FID investigations of sample chemicals, quantification was completed.

Quantitative Analysis of Phenolic Compounds Using LC-HRMS

Due to their ability to act as antioxidants, phenolic chemicals were also significant. The aerial part of *Thymus brachychilus* were analyzed using LC-HRMS. In a 6 mL volumetric flask, the dried 60 mg extracts of each species were dissolved in water and ethanol (40:60). Until a clear solution was attained, the flask was held in an ultrasonic bath. The volume was then diluted with mobile phase before 100 µL of dihydrocapsaicin solution (from a 100 ppm stock solution) was added as internal standard. It was mixed and warmly heated to clarify a resolution. The final concentration of the solution (1 mL) was put into a sealed auto sampler vial after being filtered with a 0.45 µm Millipore Millex-HV filter. For each run, 2 µL of the sample was then injected into LC. Throughout the experiment, the samples in the auto sampler were maintained at 15 ºC.

Thermo ORBITRAP Q-EXACTIVE (Bremen, Germany) mass spectrometry-equipped ESI ion source and Dionex LC equipment were used for the LC-HRMS measurements. The scan range was adjusted to m/z 100-900 amu, and the following mass parameters were used: capillary temperature was 320 °C, aux gas heater temperature was 320 °C, gas flow rate was 45, aux gas flow rate was 10, sprey voltage was 3.80 kV, and Slens RF was 50. Compound separation was performed by using a Troyasil C18 column (150x3 mm i.d., 5 µm particle size, İstanbul, Turkey). The mobile phases A and B contained 1% formic acid in water and 1% formic acid in methanol, respectively. The gradient program was 50% A and 50% B for the first 0-1.00 min, 100% B for the next 1.01-6.00 min, and 50% A and 50% B for the final 6.01-15 min. The column temperature was set to 22 ºC, and the mobile phase flow rate was 0.35 mL/min. Compounds were identified by contrasting the HRMS data from the Bezmialem Vakıf University, Drug Application and Research Center Library-ILMER with the retention periods of reference compounds (in the purity range of 95-99%; see section chemicals). Dihydrocapsaicin (purity 95%) was employed as an internal standard for LC-HRMS measurements in order to decrease the repeatability problem brought on by external factors, such as ionization repeatability, in mass spectrometry studies. Table 2 provides the specific mass parameters of each target chemical.

Cytotoxicity Activity Assays

The following chemicals were bought from Sigma Aldrich: dimethyl sulfoxide (DMSO), 2.5-diphenyl-2H-tetrazolium bromide (MTT) (St. Louis, Missouri, USA). The following items were acquired from Wisent INC: Fetal bovine serum (FBS), phosphate buffer solution, high glucose Dulbecco's Modified Eagle Medium (DMEM), F12 cell culture medium, and trypsin/EDTA solution (Quebec, Canada).

The cytotoxicity of the ethanol extract and EO of *Thymus brachychilus* was assessed using the MTT assay. MTT assay is one of the most frequently referred test in cytotoxicity evaluation. In this test, the water-soluble yellow MTT pigment metabolized by the active mitochondrial enzymes in the viable cells to produce a water-insoluble purple formazan. The absorbance of light by formazan after dissolving in DMSO used to calculate the viability and then the cell death ratio. To apply the test, cells were seeded in a 96-well plate ($1x10^4$ cells/100 µL/ well), allowed to be attached overnight, then the medium was removed, and a new fresh medium containing different concentrations of the extract or the EO was added. After 24 hours exposure period, 20 µL/ well of MTT (0.5 mg/mL) were added and incubated for further 3 hours. Then, the supernatants were thrown, and formazan crystals were dissolved in 100 µL/well of DMSO, and the absorbance (OD) was measured by a Thermofisher microplate reader (Massachusetts, USA) at 590 nm. The ratio of the viable and dead cells were calculated compared to the solvent group (1% DMSO), and the results were expressed as half maximal inhibitory concentration (IC50), the concentration caused the death in one-half of the cells.

Results

Essential Oil Yield and Composition

0.42 mL of EO was obtained from 100 g dried aerial part with 0,42% (v/w) yield of *Thymus brachychilus*, density of 0.8885 g/cm^3 at 20 °C, and 99.71% of the EO was made up of 20 identified and quantified components. The four main components of the EO were determined to be thymol, which made up 48.11% of the oil, 12.92% *p*-cymene, 11.14% carvacrol, and 9.36% *endo*-borneol. The EO's chemical composition is shown in Table 1 and Figure 1.

Quantitative Analysis of Phenolic Compounds Using LC-HRMS

In this study, a total of 18 phenolic compounds were quantitatively determined by LC-HRMS in the ethanol extracts of the aerial part of *Thymus brachychilus*. According to the

results presented in Table 1, 6-methoxyapigenin-7-glucoside (10.2080±0.0052 mg/g), rosmarinic acid (9.8926±0.0038 mg/g), luteolin-7-glucoside (5.5110±0.0041 mg/g), caffeic acid (2.7753±0.0037 mg/g), and kaempferol (2.0358±0.0036 mg/g) were shown to be the primary ingredients in the aerial section of the *Thymus brachychilus* extract.

Cytotoxicity Activities

Both the ethanol extract and the EO of *Thymus brachychilus* caused cell death in the tested cell lines. However, the extract appeared to be more effective compared to the essential oil. For the extract, the IC50 values were calculated to be between 1.64-15.76 µg/mL. While the values of IC50 were calculated between 68.94-101.2 µg/mL for the essential oil. Besides that, a difference between the cell types could be seen, where the U118 MG neuronal cells appeared to be the most sensitive cell line (Table 3, Figure 2,3).

Table 1. Chemical composition of *Thymus brachychilus* essential oil

No	Components	KI[a]	RRI[b]	Relative %	Identifaction method
1	α-pinene	1012-1039	1027	1.63±0.05	RRI, MS
2	Camphene	1057-1083	1072	2.53±0.08	RRI, MS
3	β-myrcene	1145-1169	1160	0.43±0.03	RRI, MS
4	α-terpinene	1170-1201	1181	0.80±0.04	RRI, MS
5	γ-terpinene	1238-1253	1248	2.92±0.07	RRI, MS
6	*p*-cymene	1261-1290	1274	12.92±0.20	RRI, MS
7	1-octen-3-ol	1430-1460	1452	0.19±0.00	RRI, MS
8	*cis*-sabinene hydrate	1438-1474	1465	1.00±0.01	RRI, MS
9	Camphor	1490-1535	1511	1.26±0.01	RRI, MS
10	*trans*-sabinene hydrate	1542-1556	1548	0.23±0.10	RRI, MS
11	4-terpineol	1590-1635	1600	0.75±0.01	RRI, MS
12	Verbenol	1665-1686	1676	0.26±0.00	RRI, MS
13	*endo*-borneol	1696-1705	1699	9.36±0.02	RRI, MS
14	β-bisabolene	1715-1748	1727	1.11±0.46	RRI, MS
15	Carvacrol acetate	1868-1908	1902	3.61±0.04	RRI, MS
16	Thymoquinone	NA	1918	0.15±0.01	RRI, MS
17	*tau*-cadinol	2036-2184	2100	0.48±0.01	RRI, MS
18	Thymol	2153-2187	2184	48.11±0.66	RRI, MS
19	Carvacrol	2186-2239	2214	11.14±0.24	RRI, MS
20	α-cadinol	2201-2259	2230	0.83±0.02	RRI, MS
	Total identified			99.71	

RRI[b]: Relative retention indices calculated against n-alkanes; % calculated from FID data.
Identification method based on the relative retention indices (RRI) of compounds on the HP innowax column, MS, identification was performed on the basis of computer matching of the mass spectra with those of the Wiley and MassFinder libraries and comparison with literature data (15-20).
[a]KI were given from literature with confidence intervals 50% of RI data ranges for each compound
NA: Not available current literature

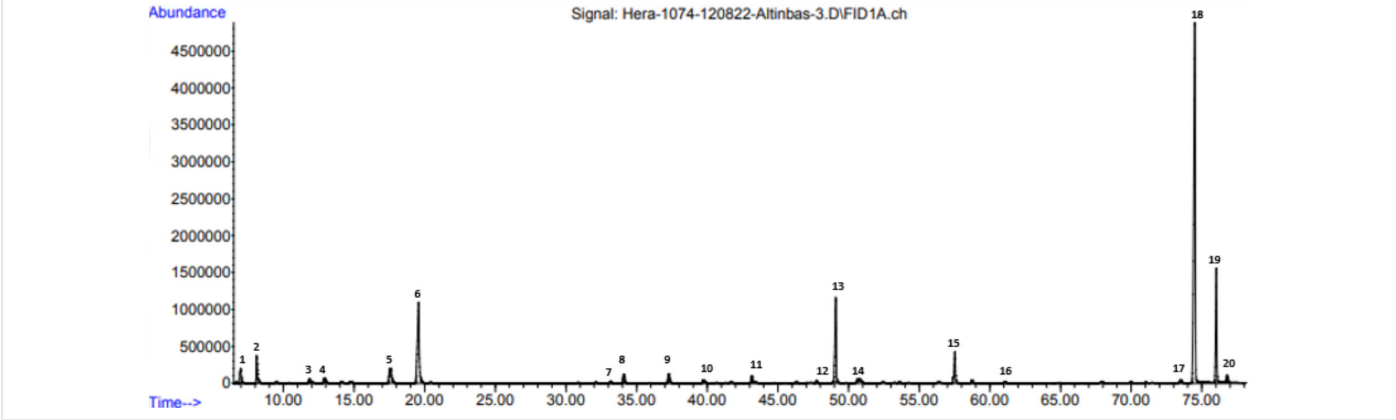

Figure 1. GC-FID chromatogram of Thymus brachychilus essential oil major compounds

Discussion

The chemical content of *Thymus* species, besides their ethnobotanical and folk medicine applications, encourage the researchers to evaluate their biological activity in general and cytotoxic effects in particular. Apigenin, chrysin, and lutein have promising futures as potent antitumor medicines for cervical cancer. For the treatment of gastric and ovarian cancer, respectively, kaempferol, lutein, and apigenin could be viewed as viable candidate medicines. The cells from the colon and liver, which are the primary sites of flavonoid metabolism, exhibit quite considerable swings in anticancer activity, which is likely caused by exposure to numerous metabolites with varied actions. The same appears to be true for chrysin, and compared to melanoma and lung cancer cells, apigenin is possibly more sensitive and effective at killing cervical cancer cells. Both cervical cancer and melanoma cell lines exhibit high levels of luteolin activity, demonstrating that these flavones may have promising futures as the active ingredients in potent anticancer drugs for the specified target areas (21). According to studies, flavonoids such chrysin,

Table 2. Quantitative analysis of phenolic compounds using LC-HRMS

No	Analyte	RT[a]	Quantification (mg/g)[b]	Polarity (ESI)	m/z
1	Ascorbic acid	2.19	0.3444±0.0039	Negative	175.0248
2	Chlorogenic acid	2.46	0.1626±0.0036	Negative	353.0878
3	Fumaric acid	2.48	0.3608±0.0029	Negative	115.0037
4	Caffeic acid	3.07	2.7753±0.0037	Negative	179.0350
5	Luteolin-7-glucoside	3.58	5.5110±0.0041	Negative	447.0933
6	Luteolin-7-rutinoside	3.62	0.4101±0.0031	Negative	593.1511
7	Hyperoside	4.40	0.0546±0.0035	Negative	463.0882
8	Rosmarinic acid	4.52	9.8926±0.0038	Negative	359.0772
9	6-Methoxyapigenin-7-glucoside	4.79	10.2080±0.0052	Negative	461.1089
10	Apigenin-7-glucoside	4.83	0.0413±0.0036	Negative	431.0984
11	Quercetin	5.66	0.0236±0.0029	Negative	301.0354
12	Salicylic acid	5.66	0.5360±0.0019	Negative	137.02442
13	Naringenin	5.70	0.0988± 0.0042	Negative	271.0612
14	Luteolin	5.81	0.9749±0.0034	Negative	285.0405
15	Kaempferol	5.81	2.0358±0.0036	Negative	285.04046
16	Apigenin	6.15	0.2724±0.0029	Negative	269.0456
17	Chrysoeriol	6.18	0.3542±0.0061	Negative	299.0561
18	Acacetin	7.07	0.0401±0.0040	Negative	283.0612

[a]RT: Retention time, [b]Values in mg/g (w/w) of plant

Table 3. The cytotoxic effects of *Thymus brachychilus* extract and essential oil in different cell lines

Cell line	IC_{50}	
	Extract (µg/mL)	Essential oil (µg/mL)
MCF-7	2.02	101.2
A549	15.76	79.86
U-118 MG	1.64	68.94

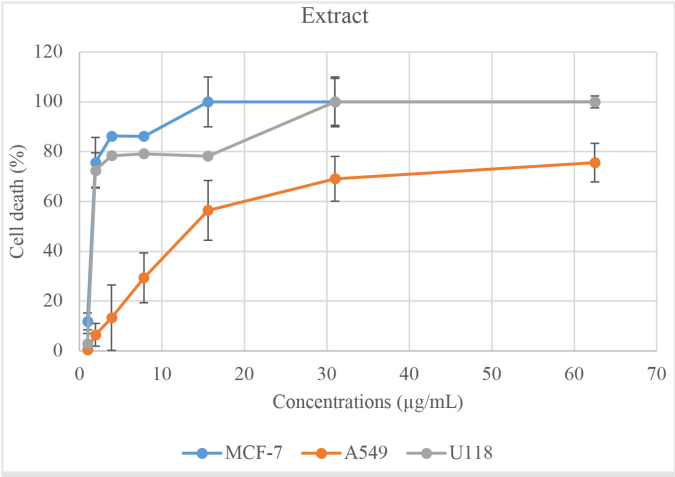

Figure 2. Cytotoxic effect of *Thymus brachychilus* extract in different cell lines

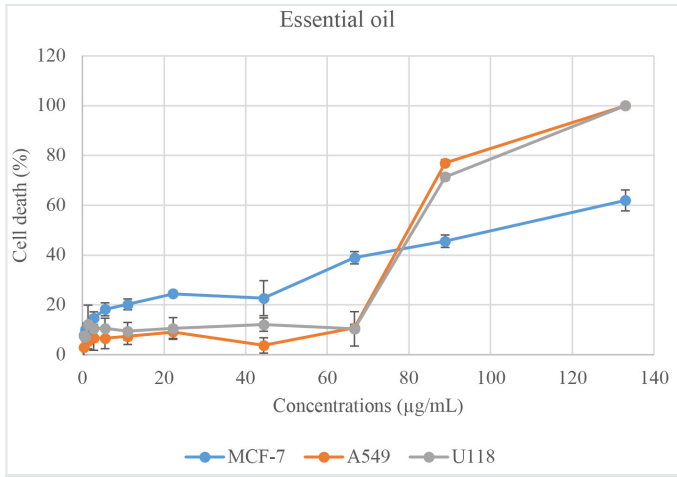

Figure 3. Cytotoxic effect of *Thymus brachychilus* essential oil in different cell lines

epigallocatechin-3-gallate (EGCG), formononetin, hispidulin, icariin, quercetin, rutin, and silibinin work in concert to boost the effectiveness of conventional chemotherapeutics. The regulation of intracellular signaling pathways involved in apoptosis, proliferation, autophagy, motility, and chemoresistance mediates these favorable effects. In light of this, flavonoids show potential in enhancing current therapeutic approaches and ultimately overcoming medication resistance in glioblastoma (GBM) (22). The chance of tumor development in numerous human organs, including stomach, colon, liver, breast, and leukemia cells, has also been found to be reduced by rosmarinic acid and some isolated chemicals from rosemary extract, such as carnosic and ursolic acids and carnosol (23).

The EO's five primary constituents were identified as being thymol, which made up 48.11% of the oil, 12.92% *p*-cymene, 11.14% carvacrol, and 9.36% *endo*-borneol, respectively. *Thymus* species are known for their rich EO content. There are also different chemotypes of the same species. When we compared our study with the studies on EO contents of other *Thymus* species, it was observed that they had similar properties with *Thymus* species, especially those with high thymol content. *Thymus ciliatus* Desf. has 79.1% thymol, 4.4% carvacrol (24), *Thymus kotschyanus* Boiss. has 22.75% carvacrol, 16.52% thymol, 11,39% thymoquinone, 4.52% borneol (25), *Thymus praecox* subsp. *scorpilii* (Velen) Jalas var. *laniger* (Borbas) Jalas has 69.09% thymol, 5.54% borneol, 3.08% carvacrol (26), *Thymus daenensis* Čelak. subsp. *daenensis* has 74.7% thymol, 1.3% carvacrol (27), *Thymus pulegioides* L. has 63.2% carvacrol, 15.55% thymol (28), *Thymus serpyllum* L. has 46.24% thymol, 9.43% thymoquinone, 1.34% borneol (29) in their EO.

Thymus vulgaris is one of the famous herbs evaluated for its biological activity. According to the Scopus database (27.11.2022), there are 69 papers containing the words *Thymus vulgaris* and "cytotox" in their abstract section [ABS (*Thymus* AND *vulgaris*) AND ABS (cytotox)], and 144 paper containing the words *Thymus vulgaris* and "cytotox" in their title, abstract or keywords section [TITLE-ABS-KEY (*Thymus* AND *vulgaris*) AND TITLE-ABS-KEY (cytotox)]. These studies reported that *Thymus vulgaris* extracts, essential oils, and its isolated compounds were evaluated in A549 cells, oral cavity squamous cell carcinoma, human breast cancer (SK-Br-3), head and neck squamous cell carcinoma, human breast cancer cell line (MDA-MB-231), human colon adenocarcinoma cell line (Caco-2), human hepatocellular carcinoma cell line (HepG2), THP-1, U937, and K562 leukemia cell lines, human cervical cancer (HeLa) cell line, porcine liver primary cell culture, human breast cancer (MCF-7) cell line, human prostatic adenocarcinoma (PC3) cell line, and other cells (Table 4). Results, in general, indicated the cytotoxicity and anti-cancer activity of *Thymus vulgaris* (30-38). The IC50 was calculated to be 10.50±0.01 µg/mL after 72 h on the A549 cells for *T. vulgaris* L. EO which had thymol (41.33%), 1.8-cineole (24.10%) (34). According to Nikolić et al. (35) *Thymus serpyllum* EO which had thymol (56.02%), carvacrol (14.00%) and *p*-cymene (6.2%) has cytotoxicity with IC50 value 52.69±3.28 µg/mL in MCF7, 17.71±3.23 µg/mL in HeLa, 34.96±2.90 µg/mL in HepG2, *T. algreriensis* EO which had thymol (38.5%), *p*-cymene (8.9%), terpinene (7.1%), bornyl acetate (7.0%), borneol (6.0%) had cytotoxicity with IC50 value 62.53±1.88 µg/mL in MCF7, 64.79±1.51 µg/mL in HeLa, 62.12±3.11 µg/mL in HepG2.

However, the other species of *Thymus*, especially the endemic ones, have different content and so different biological effects. Previous studies in similar species in terms of chemical compositions concluded the cytotoxicity of the tested species (Table 4). The cytotoxicity of *Thymus pulegioides* L. was tested on Caco-2 and HepG2 cell lines. The IC50 was calculated to be 137.4 µg/mL for the aqueous decoctions and 147.4 µg/mL for the hydro-ethanolic extracts in Caco-2 cells and to be more than 500 µg/mL in HepG2 cells (39). *Thymus kotschyanus* extract and essential oils which had carvacrol (27.8±4.68), thymol (16.8±2.10), thymoquinone (5.4±0.40) were evaluated in HeLa and A549 cell lines, data reported the cytotoxicity with IC50 values varied between ≤0.15-≤0.31 µg/mL (33,40). *Thymus daenensis* extracts and essential oils which had 70.12±8.24% thymol, 4.99±0.68% carvacrol were also reported to have cytotoxicity in different cells,

with IC50 equal to 203.6 µg/mL in HepG2 cells, 4.95 µg/mL in HeLa cells and 1455 µg/mL in human normal lymphocytes (40-42). Other species essential oils such as *Thymbra capitata* (L.) Cav. (Carvacrol 71.4%) , *Thymus caespititius* Brot. (carvacrol 45.5 %, thymol 10.3%) (from different five site) reported to have cytotoxicity with IC50 between 200-250 µg/mL in leukemia (THP-1) cells, while *Thymus mastichina* (L.) L. (1.8-cineole 47.4%, thymol 13.7%), *Thymus pulegioides* L. (geraniol 32.8%, carvacrol 12.4%, thymol 12%), and *Thymus villosus* subsp. *lusitanicus* (Boiss.) Cout. (linalool 65.5%) had lower cytotoxic

Table 4. The cytotoxic effects of some *Thymus* species

Species name	Sample type	Cell line	Results	References
Thymus alpestris Tausch ex A.Kern.	Fresh leaves in phosphate Buffer (1:19, w/w)	Human erythrocytes	Mild cytotoxic effect at 5 and 0.5 mg/mL.	(43)
Thymus pannonicus All.				
Thymus porcii Borbás				
Thymus daennesis Čelak.	Essential oils	Human normal lymphocytes	1455 µg	(42)
		HeLa cells	4.95 µg	
Thymus serpyllum L.	Methanol extract	MCF-10A cells	not cytotoxic	(44)
		MCF-7 cells	509 µg/mL (72 hours exposure)	
		MDA-MB-231 cells	276 µg/mL (72 hrs)	
Thymus kotschyanus Boiss & Hohen	Ethanolic extract	HeLa cells	≤0.31 mg/mL after 24 hrs ≤0.08 mg/mL after 48 hrs	(33)
		A549 cells	≤0.15 mg/mL after 24 hrs ≤0.08 mg/mL after 48 hrs	
Thymus caramanicus Jalas	Essential oil	Human Oral Epidermoid Carcinoma KB Cells	0.44 µL/mL	(45)
	Leaves hydro-ethanolic extract		105 µg/mL	
Thymus daenensis Celak	Herbs hydro-methanolic Extracts	HepG2 cell	203.6 µg/mL	(41)
Thymus daenensis Celak	Essential oil, Final exposure concentration 1%	HeLa cells	≤55% cell death after 72 hrs	(40)
Thymus vulgaris L.			≤75% cell death after 72 hrs	
Thymus kotschyanus Boiss & Hohen			≤75% cell death after 72 hrs	
Thymus broussonettii Boiss.	Essential oil	Human ovarian adenocarcinoma IGR-OV1 parental cell line OV1/P	0.4%	(46)
		Its chemoresistant counterparts OV1/adriamycin (OV1/ADR)	0.39%	
		OV1/vincristine (OV1/VCR)	0.94%	
		OV1/cisplatin (OV1/CDDP)	0.65%	
Thymus pulegioides L.	Decoction	HepG2 cells	>500.00 µg/mL	(39)
		Caco-2 cells	137.7 µg/mL	
	Hydroethanolic extracts	HepG2 cells	>500.00 µg/mL	
		Caco-2 cells	148.7 µg/mL	
Thymbra capitata (L.) Cav.	Essential oil	THP-1 cells	IC_{50} btw 200-250 µg/mL	(47)
Thymus caespititius Brot.			IC_{50} btw 200-250 µg/mL (the effect varies according to the site of collection)	
Thymus mastichina L.			≥450 µg/mL	
Thymus pulegioides L.			≥450 µg/mL	
Thymus villosus subsp. *lusitanicus* (Boiss.) Cout.			≥450 µg/mL	

effects with IC50 ≥450 µg/mL (47). *Thymus serpyllum* extracts, essential oils which had 46.24% thymol, 9.43% thymoquinone, 1.34% borneol and isolated compounds were evaluated for the cytotoxic effects in human normal breast (MCF-10A), MCF-7, MDA-MB-231, HepG2, human colon cancer (HCT-116), PC3, and A549 cell lines; the results concluded the cytotoxic and so the anti-cancer effect of the tested herb (44,48,49).

Thymus brachychilus, according to the chemical content, is believed to have effects similar to the mentioned species in Table 4. For that, the cytotoxic effects of the ethanol extract and the EO of *Thymus brachychilus* were evaluated by MTT assay in A549, MCF-7, and U118-MG cancer cell lines. Results indicated the IC50 values were between 1.64-15.76 µg/mL for the extract and between 68.94-101.2 µg/mL for the EO.

Study Limitations

Since there is no previous study on the content of *Thymus brachychilus* EO and extract, the results obtained could not be compared with other studies. However, in the future, it is planned to carry out analysis studies on the chemical content of samples of *Thymus brachychilus* collected in different months.

Conclusion

The conducted study indicates that ethanolic extract and essential oils of *Thymus brachychilus* have potential antiproliferative properties on human breast adenocarcinoma (MCF-7, HTB-22), human lung adenocarcinoma (A549, CRM-CCL-185), and human GBM cells (U-118 MG, HTB-15) cells and may be used as a candidate for further studies. However, the exact molecular mechanism or mechanisms underlying the anticancer effects of *Thymus brachychilus* need to be clarified in further research. *Thymus brachychilus* ethanolic extract contains polyphenols responsible for its observed anticancer effect in this study. As a result of their antioxidative and potential anticarcinogenic properties, dietary phenolics are currently generating a lot of interest. Additionally, phenolic acids and flavonoids serve as reducing agents, free radical scavengers, and inhibitors of the formation of singlet oxygen. Moreover, components like flavonoids and phenolic acids are crucial in the prevention and treatment of cancer as well as other human disorders.

These results confirm the similarity in the activity with the other species and lighten the possibility to be used in the research and development of new anticancer drugs. This study has shown that 6-methoxyapigenin-7-glucoside, rosmarinic acid, luteolin-7-glucoside, caffeic acid, and kaempferol can all be found in *Thymus brachychilus* as good renewable biosources. The EO of *Thymus brachychilus* reduces the viability of a number of tumor cell lines in a concentration-dependent way. The particular oil constituent are typically held responsible for the oil's activity. One key limitation of the study is that it is yet unclear whether thymol acts alone or in concert with other oil constituents to cause the cytotoxicity against tumor cells that has been reported.

Ethics

Ethics Committee Approval: Our study does not require ethics committee approval.

Informed Consent: Our study does not require informed Consent.

Peer-review: Externally peer reviewed.

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Original Article

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Evaluation of Quality of Life and Functional Status in Elderly Patients with Rheumatoid Arthritis

Yaşlı Romatoid Artritli Hastalarda Yaşam Kalitesi ve Fonksiyonel Durumun Değerlendirilmesi

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ABSTRACT

Objective: This study was conducted to evaluate quality of life, functional status and pain in elderly patients with rheumatoid arthritis (RA).

Methods: The sample of this study consisted of 229 outpatients followed up in the rheumatology department of a hospital with a diagnosis of RA and those over 65 years old who were treated in the internal medicine clinic of the same hospital. Research data were collected using a Personal Introduction Form, the Disease Activity score 28 (DAS-28), the Numerical Pain Assessment Scale, the Health Assessment Questionnaire (HAQ) and the SF-36 Quality of Life scale.

Results: The physical conditions of the non-RA elderly individuals were statistically worse compared to those with RA (p=0.01). There was a significant negative correlation between patient age and visual analog score, physical function, physical role limitations, emotional role limitations and social functionality subscale scores, and a significant positive correlation between age and HAQ scores (p<0.05).

Conclusion: In the study, elderly patients with RA had fewer physical limitations in daily activities and their severity of pain was not different than that of adult patients with RA. The physical and social functionality of the elderly who had received treatment due to a chronic disease other than RA had lower physical and social functionality, but their quality of life was better.

Keywords: Elderly patients, functional status, quality of life, rheumatoid arthritis

ÖZ

Amaç: Bu çalışma, yaşlı romatoid artritli (RA) hastalarda yaşam kalitesi, fonksiyonel durum ve ağrıyı değerlendirmek amacıyla yapıldı.

Yöntemler: Araştırmanın örneklemini bir hastanenin romatoloji polikliniğinde RA tanısı iletakip edilen 229 hasta ile aynı hastanenin dahiliye kliniğinde tedavi gören 65 yaş üstü hastalar oluşturdu. Araştırma verileri Kişisel Tanıtım Formu, Hastalık Aktivite Puanı 28 (DAS-28), Sayısal Ağrı Değerlendirme Ölçeği, Sağlık Değerlendirme Anketi (HAQ) ve SF-36 Yaşam Kalitesi Ölçeği kullanılarak toplanmıştır.

Bulgular: RA tanısı olmayan yaşlı bireylerin fiziksel durumları RA tanısı olanlara göre istatistiksel olarak daha kötüydü (p=0,01). Hasta yaşı ile görsel analog skoru, fiziksel fonksiyon, fiziksel rol kısıtlılıkları, emosyonel rol kısıtlılıkları ve sosyal işlevsellik alt ölçek puanları arasında negatif; yaş ile HAQ puanları arasında pozitif yönde anlamlı korelasyon saptandı (p<0,05).

Sonuç: Çalışmada yaşlı RA'lı hastaların günlük aktivitelerinde daha az fiziksel kısıtlamaları olduğu ve ağrı şiddetlerinin erişkin RA'lı hastalardan farklı olmadığı görüldü. RA dışında kronik bir hastalık nedeniyle tedavi gören yaşlıların fiziksel ve sosyal işlevselliklerinin daha düşük, yaşam kalitelerinin ise daha iyi olduğu görüldü.

Anahtar Sözcükler: Yaşlı hasta, fonksiyonel durum, yaşam kalitesi, romatoid artrit

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Introduction

Rheumatoid arthritis (RA) is a frequently seen systemic autoimmune disease of the musculoskeletal system, primarily affecting the synovial joint leading to progressive disability (1). The disease is mostly seen between the ages of 20-50, and occasionally in older people (2). Approximately 30% of RA cases occur in old age and that rate is increasing every day worldwide (3). The elderly RA population consists of both individuals who develop RA at an advanced age and patients diagnosed as having RA early in life (4). The occurrence of the disease at age 60 and above is defined as late-onset or elderly-onset RA (5). Old age related physiological changes and RA that occurs in advanced ages cause a decrease in functional capacity (6). In studies, patients with late-onset RA were reported to have more prominent and acute symptoms and higher disease activity than patients with early-onset RA (7,8). Some studies, on the other hand, have reported that the response to anti tumor necrosis factor-alpha (TNF- α) drugs used in the treatment of RA varies according to age groups, and that the response is better in young people (9). Though, the reason for this difference between age groups in terms of disease activity cannot be fully explained.

Chronic inflammation and pain often lead to a decrease in physical activity and functional disabilities in patients with RA (10) and a significant reduction in the quality of life (11,12). Low quality of life is associated with high disease activity and functional disability (13,14). Since functional disability is associated with disease activity and radiographic joint damage, functionality is frequently used as an outcome to evaluate the effect of RA over time (15). In a study conducted with an Asian population, it was found that patients with late-onset RA had a worse functional status due to comorbidities than patients with early-onset RA. On the other hand, despite their poor physical functionality, patients with late-onset RA were reported to cope better emotionally and mentally than patients with early-onset RA (16). In another study comparing disease activity and the quality of life of patients with RA both under and over 60, it was determined that the physical health and physical functions of elderly patients with RA were worse and that their quality of life was more negatively affected (17).

Individuals have difficulty in fulfilling their daily activities due to physical dependence and functional regression with old age. With aging, the quality of life deteriorates due to disease-related complications, comorbidities, social or economic problems, and changes in daily life activities (18,19). In another study examining the relationship between age and quality of life in individuals with RA, it was reported that elderly patients with RA, similar to the general population, had lower quality of life scale scores in terms of physical activity than younger patients with RA (20). Health professionals should be aware of disease-related inflammatory changes and old age-related physiological changes while ensuring the follow-up and care of elderly patients with RA. In this study, the functionality and quality of life of elderly patients with RA was evaluated by comparing with younger patients with RA and elderly non-RA individuals.

Methods

Study Design

This descriptive study aims to evaluate quality of life, functional status and pain in elderly patients with RA.

Research Place

Research was carried out at the rheumatology outpatient clinic and internal diseases clinic of university hospital after obtaining permission from the ethics committee and the institution.

Sample

The sample of the study consisted of patients who were over 18, treated and monitored due to a diagnosis of RA in the outpatient and internal clinic of the rheumatology department, and patients aged 65 being treated in the internal diseases clinic of university hospital. All included were literate and agreed to participate in the study (Figure 1).

According to an age classification of the World Health Organization (www.healthindicators.org), RA patients between 18-65 formed the adult group, patients over 65 constituted the elderly group and individuals over 65 who had been treated for any other health issue in the internal medicine clinic formed the non-RA elderly group. A power analysis was used to determine the size of the research sample. In calculating the sample, the results of the study conducted by Koçyigit et al. (21) were used as reference and the size of the sample was determined as 225 units, 75 units in each group, with a power of 80%, type I error of 5% and medium effect size (ES =0.3). The study was completed with a total of 229 patients (21).

Exclusion criteria of the research

- Patients with a variable level of consciousness (changes in consciousness such as confusion, stupor, dementia),
- Patients with a known psychiatric disorder,
- Patients with severe hearing or visual impairment,
- Patients who did not agree to participate in the study were not included.

Data collection method and data collection tools

In the study, patients who met the inclusion criteria were informed by a researcher and written consent was obtained. A Personal Introduction Form developed by researchers according to available literature, the Disease Activity Score 28 (DAS-28), the Numerical Pain Assessment Scale, the Health Assessment Questionnaire (HAQ) and the Short Form of Survey-36 (SF-36) Quality of Life Scale were implemented to patients using via face-to-face interview.

Personal introduction form: this form was developed by researchers according to the literature (22,23) and consisted of 18 questions on socio-demographic characteristics, disease and treatment.

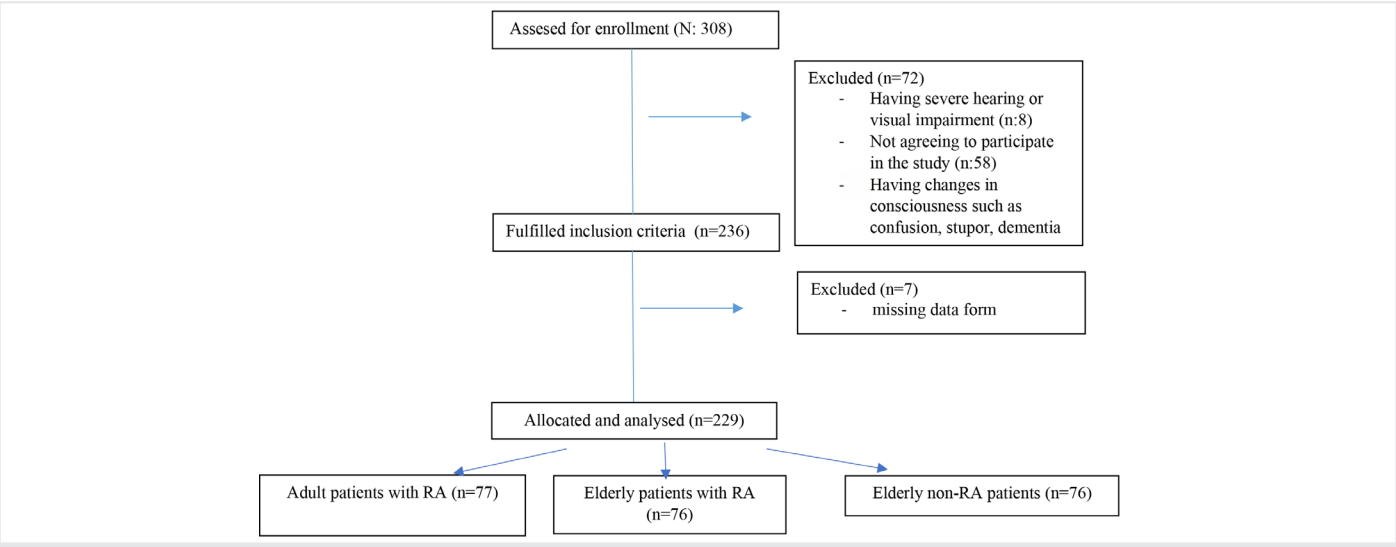

Figure 1. Subjects' recruitment flow diagram

Disease activity score 28 (DAS-28): This is a score routinely used during RA exams to evaluate disease activity in which 28 joints are assessed for tenderness and swelling. A value of 2.6 and below is evaluated as remission, between 2.6-3.2 is considered low disease activity, between 3.2-5.1 is moderate activity and a value above 5.1 is high disease activity (24). In this study, the level of disease activity was determined using this score during physical examination.

Numerical pain assessment scale: This scale, which aimed to assess the severity of patient pain, was used to explain the pain in numbers. On the scale, a score of 0 indicates no pain and 10 confers excruciating pain (25).

Health assessment questionnaire (HAQ): The HAQ was developed by Fries et al. in 1980 to evaluate the physical limitations of patients with RA. It gauges activities of daily living consisting of 20 items in 8 sections. Each item is scored between 0-3 (0: no difficulty at all, 1: some difficulty, 2: great difficulty, 3: cannot do it at all). The scale was adapted to our society and Cronbach's alpha coefficient was 0.97 (26).

SF-36 quality of life scale: SF 36 is one of the most common metrics used to measure quality of life. It was developed by Ware et al. in 1992. Turkish validity and reliability study of this scale was performed by Koçyigit et al. (21) The short form of the scale consists of 36 items and 8 subscales, which are: physical function, social function, mental health, physical role limitations, emotional role limitations, vitality/energy, pain, and general health perception. Subscales evaluate health between 0 and 100, with a score of 0 indicating poor health and a score of 100 showing good health. Koçyigit et al. (21) found that Cronbach's alpha values of the subscales were between 0.73-0.76.

Statistical Analysis

A statistics package program was used in the analysis of data obtained in the study. Shapiro-Wilk test was used to examine the conformity of quantitative variables to normal distribution and it was determined that the quantitative variables were not normally distributed. The summary values of the non-normally distributed quantitative variables were shown as the median (Q1-Q3). Intergroup distributions of quantitative variables with no normal distribution were compared with Kruskal-Wallis and Mann-Whitney U tests. Qualitative variables were expressed with frequency and percentage, and the relationship between qualitative variables was evaluated with the pearson chi-square test. Spearmen's test was used to evaluate the correlation between variables. Results with a p-value of <0.05 were considered significant.

Ethical Approval

Ethics committee approval dated 15.05.2018 with number 17 was obtained from the non-interventional ethics committee of a university and written consent from the relevant institution. The researchers informed all patients about the study and obtained written consent from them that they wanted to participate in the study. The patients were told that their participation in the study was entirely at their own discretion and that they could refuse to participate or withdraw from the study at any time. When they wanted to withdraw from the study, they were informed that the treatment planned by their physician would not be interrupted or changed.

Results

Patients' Sociodemographic and Medical Characteristics

When the sociodemographic and medical characteristics of the patients participating in the study were compared, there were statistically significant differences in all three groups in terms of gender, education level, profession, receiving care from family members, employment status, social security, smoking, hypertension, diabetes mellitus, chronic kidney disease, and coronary artery disease ($p<0.05$) (Tables 1, 2). More than half of the patients in all three groups were female (51.3%) and primary school graduates (56.8%), the majority were married (76.9%),

Table 1. Distribution of socio-demographic characteristics of patients according to groups

Socio-demographic characteristics		Adult patients with RA		Elderly patients with RA		Elderly non-RA patients			
		Median (Q1-Q3)		Median (Q1-Q3)		Median (Q1-Q3)		p	
Age		56 (51-62)		70 (66-73.5)		71 (66.5-75.5)		<0.001	
		n	%	n	%	n	%	X^{2*}	p
Gender	Female	64	83.1	53	69.7	39	51.3	17.949	**<0.001**
	Male	13	16.9	23	30.3	37	48.7		
Marital status	Married	62	79.6	57	75	57	74.1	1.835	0.766
	Single	15	19.5	19	25	19	25		
Education level	Literate	6	7.8	11	14.5	22	28.9	33.843	**<0.001**
	Primary school	39	50.6	50	65.8	41	53.9		
	Secondary school	9	11.7	7	9.2	5	6.6		
	High school	14	18.2	3	3.9	1	1.3		
	University	9	11.7	5	6.6	7	9.2		
Receiving care from family members	Yes	9	11.7	21	27.6	50	65.8	51.921	**<0.001**
	No	68	88.3	55	72.4	26	34.2		
Caring for family members	Yes	26	33.8	19	25	17	22.4	2.765	0.251
	No	51	66.2	57	34.1	59	77.6		
Job	Officer	10	13	0	0	2	5.2	40.899	**<0.001**
	Employee	9	11.7	2	2.6	0	0		
	Retired	15	19.5	32	42.1	39	51.3		
	Self-employment	4	5.2	1	1.3	4	5.3		
	Housewife	38	49.4	40	52.6	31	40.8		
	Farmer	1	1.3	1	1.3	0	0	27.488	
Employment status	Yes	19	24.7	2	2.6	2	2.6		**<0.001**
	No	58	75.3	74	97.4	74	97.4	18.429	
Social security	Yes	70	90.7	75	98.7	68	89.5		**0.018**
	No	7	9.1	1	1.3	8	10.5		
Income status	Income does not meet the expenditure	26	33.8	16	21.1	23	30.3	7.574	0.108
	Income is equal to the expenditure	44	57.1	57	75	51	67.1		
	Income meet the expenditure	7	9.1	3	3.9	2	2.6		
Total		77	100	76	100	76	100		

*Pearson chi-square test, RA: Rheumatoid arthritis

90% were unemployed (Table 1). The rate of smoking was higher in adult patients with RA (23.4%). The rates of hypertension (53.9%), diabetes mellitus (53.9%), chronic kidney disease (18.4%) and coronary artery disease (23.7%) were higher in elderly non-RA individuals (Table 2). The median ages of adult patients withRA, elderly patients with RA and elderly non-RA individuals were 56 (51-62), 70 (66-73.5) and 71 (66.5-75.5), respectively.

The median durations of disease in adult and elderly patients with RA were 9 (5-15) and 14 (5-19.5) years, respectively. While adult patients with RA had been receiving treatment for an average of 8 years, elderly patients with RA had been receiving treatment for an average of 12 years. The duration of disease and the treatments used were statistically different ($p<0.05$) but disease activity scores (DAS-28 score) and duration of treatment were similar ($p>0.05$) among the groups. Patients with RA in both groups mostly received antirheumatic therapy (47.6%) and biologic agents (22.2%) (Table 2).

Comparison of Patients' VAS, HAQ, and SF-36 Quality of Life Scale Scores

The severity of pain of the patients with RA in our study was moderate according to VAS scores, and the severity of pain of elderly non-RA individuals was statistically lower ($p<0.001$).

The HAQ score of elderly non-RA individuals was significantly higher than that of the patients with RA. According to this result, it was determined that the physical condition of the elderly non-RA individuals was statistically worse than the patients with RA (p=0.01). It was determined that, there was a significant difference between the groups in terms of the SF-36 Quality of Life scale scores for physical role limitations, physical function, social functionality and mental health subscale (p<0.05). Adult patients with RA had significantly higher physical functionality and physical role limitation scores than elderly patients with RA and non-RA patients. The social functionality score of elderly non-RA individuals was lower than that of adult and elderly patients with RA, and their mental health score was also lower than that of elderly patients with RA (p=0.006) (Table 3).

Table 2. Medical characteristics of patients by groups

Medical characteristics			Groups: Adult patients with RA		Elderly patients with RA		Elderly non-RA patients		Total		X^{2*}	p
			n	%	n	%	n	%				
Smoking habit	Yes		18	23.4	9	11.8	5	6.6	32	14	9.408	**0.009**
	No		59	76.6	67	88.2	71	93.4	197	86		
Alcohol habit	Yes		3	3.9	4	5.3	9	11.8	16	7	4.236	0.120
	No		74	96.1	72	94.7	67	88.2	213	93		
Other chronic disease	Hypertension	Yes	16	20.8	35	46.1	41	53.9	92	40.2	19.142	**<0.001**
		No	61	79.2	41	53.9	35	46.1	137	59.8		
	Diabetes mellitus	Yes	12	20	10	13.2	41	53.9	63	26.6	33.437	**<0.001**
		No	65	84.4	66	86.8	35	46.1	166	72.4		
	Chronic kidney disease	Yes	4	5.2	5	6.6	14	18.4	23	10	8.917	**0.012**
		No	73	94.8	71	93.4	62	81.6	206	90		
	Coronary artery diseases	Yes	2	2.6	9	6.6	18	23.7	25	10.9	19.689	**<0.001**
		No	75	97.4	71	93.4	58	76.3	204	89.1		
	COPD	Yes	2	2.6	11	14.5	9	9.3	22	6.6	3.069	0.216
		No	75	97.4	65	85.5	69	90.7	214	93.4		
	Osteoarthritis	Yes	1	1.3	2	2.6	0	0	3	1.3	2.036	0.361
		No	76	98.7	74	97.4	76	100	226	98.7		
Treatment	NSAIDs	Yes	1	1.3	4	5.3	-	-	5	2.2	231.846	**<0.001**
		No	76	98.7	72	94.7	-	-	148	64.6		
	Anti-rheumatic drugs	Yes	59	76.6	50	65.8	-	-	109	47.6	232.280	**<0.001**
		No	18	23.4	26	34.2	-	-	44	19.2		
	Steroids	Yes	4	5.2	10	13.2	-	-	14	6.1	233.367	**<0.001**
		No	73	94.8	66	86.8	-	-	139	60.7		
	Biological agents	Yes	12	15.6	22	28.9	-	-	34	22.2	244.084	**<0.001**
		No	65	84.4	54	71.1	-	-	119	77.8		
			Median (Q1-Q3)		**Median (Q1-Q3)**		-		**Mann-Whitney U test**			**P**
Duration of disease (year)			9 (5-15)		14 (5-19.5)		-		2380.5			**0.046**
Duration of treatment (year)			8 (4-16)		12 (5-17)		-		2,551			0.170
DAS28 score			3.04 (2.55-3.9)		3.24 (2.59-4.03)		-		2622.5			0.268
Total			77	**100**	**76**	**100**	**76**	**100**	**229**	**100**		

*Pearson chi-square test, RA: Rheumatoid arthritis

Table 3. The distribution of HAQ, VAS and SF-36 quality of life subscale scores of patients according to groups

Scale scores	Groups Adult patients[a] of RA Median (Q1-Q3)	Elderly patients[b] with RA Median (Q1-Q3)	Elderly non-RA patients[c] Median (Q1-Q3)	Kruskal Wallis test	p*
VAS	5 (4-7)	5 (1.25-7)	2 (0-5)	17.896	**<0.001**
		a-c: 0.01 b-c: <0.001			
HAQ	0. 7(0.175-1.15)	0.65 (0.15-1.23)	1.32 (0.21-2.47)	14.622	**0.001**
		a-c: 0.02 b-c: 0.04			
SF-36 subscales					
Physical functioning	50 (30-65)	35 (16.25-60)	20 (0-53.75)	24.965	**<0.001**
		a-c: <0.001 b-c: 0.01			
Role physical	25 (0-75)	0 (0-50)	0 (0-25)	8.823	**0.012**
		a-c: 0.01			
Bodily pain	45 (32-67.5)	45 (32.5-67.5)	45 (22.5-75.6)	0.262	0.877
General health	40 (25-48.1)	40 (21.25-55)	35 (20-55)	0.455	0.796
Vitality	50 (30-60)	50 (35-55)	40 (25-55)	3.586	0.166
Role emotional	0 (0-66.6)	0 (0-33.3)	0 (0-33.3)	2.880	0.237
Social functioning	50 (37.5-75)	62.5 (50-75)	37.5 (25-62.5)	25.922	**<0.001**
		a-c: <0.001 b-c: <0.001			
Mental health	56 (40-64)	52 (48-68)	48 (36-60)	10.356	**0.006**
		b-c: 0.005			

RA: Rheumatoid arthritis

Correlation between Patients' Sociodemographic, Disease and Treatment Characteristics and VAS, HAQ, and SF-36 Quality of Life Scale Scores

In our study, there was a weak, negative significant correlation between age and VAS score (r=-0.160, p=0.015), physical function (r=-0.301, p<0.001), physical role limitations (r=-0.184, p:0.005), emotional role limitations (r=-0.151, p=0.023) and social functionality (r=-0.168, p:0.011) subscale scores. There was a weak positive significant correlation between the patient's age and HAQ score (r=0.199, p=0.002). There was a weak, positive highly significant correlation between the patient's VAS score and HAQ score (r=-0.288, p<0.001), a weak negative significant correlation between VAS score and physical role limitations (r=-0.177, p=0.007), vitality (r=-0.177, p=0.007), social functionality (r=-0.188, p=0.004) and general health perception (r=-0.288, p<0.001) subscale scores. A moderate, very significant negative correlation was found between VAS score and pain subscale score (r:-0.485, p<0.001). There was a strong negative correlation between patient's HAQ score and physical function subscale scores (r=-0.721, p<0.001), a moderate, highly significant negative correlation between HAQ score and physical role limitations (r=-0.457, p<0.001), vitality (r=-0.434, p<0.001), social functionality (r=-0.597, p<0.001), pain (r=-0.588, p<0.001) and general health perception (r=-0.463, p<0.001) subscale scores. Also, a weak very significant negative correlation between patient's HAQ score and emotional role limitations (r=-0.339, p<0.001) and mental health (r=-0.253, p<0.001) subscale scores was determined (Table 4).

The duration of disease in patients with RA was weakly positively correlated with HAQ score and negatively correlated with physical function, physical role limitations and emotional role limitations subscale scores. The duration of treatment in patients with RA, on the other hand, was weakly positively correlated with HAQ score, but weakly negatively correlated with physical function and emotional role limitations subscale scores. There was a highly significant positive correlation between the DAS-28 score and VAS score of the patients with RA (r=0.708, p<0.001), a moderate positive significant correlation between DAS-28 and HAQ scores, and a weak negative significant correlation between the DAS-28 score and physical function (r=-0.193, p=0.017), physical role limitations (r=-0.457, p<0.001), social functionality (r=-0.233, p=0.004) and pain (r=-0.395, p<0.001) scores (Table 5).

Discussion

Within the scope of the study, pain, quality of life and functional status of elderly patients with RA were all evaluated by comparing with adult patients with RA and elderly non-RA patients. Results showed that the severity of pain was lower in elderly non-RA patients than in adult and elderly patients with RA, but was not different between adult and elderly patients with RA. The fact that the severity of pain scores of patients in both RA groups were higher than the elderly individuals with chronic diseases other than RA was due to the primary characteristic of RA, pain. As a matter of fact, genetic predisposition, comorbidities such as osteoarthritis, fibromyalgia, depression, acute inflammatory

Table 4. Correlation of age, VAS, HAQ and SF-36 Quality of Life subscale scores of patients*

Characteristics		VAS	HAQ	Physical functioning	Role physical	Role emotional	Vitality	Mental health	Social functioning	Bodily pain	General health
Age	r	-0.160	0.199	-0.301	-0.184	-0.151	-0.032	-0.056	-0.168	-0.054	-0.016
	p	**0.015**	**0.002**	**<0.001**	**0.005**	**0.023**	0.625	0.398	**0.011**	0.415	0.811
VAS	r	1.000	0.288	-0.195	-0.177	-0.133	-0.177	-0.099	-0.188	-0.485	-0.288
	p	-	**<0.001**	0.003	**0.007**	0.087	0.007	0.135	**0.004**	**<0.001**	**<0.001**
HAQ	r	0.288	1.000	-0.721	-0.457	-0.339	-0.434	-0.253	-0.597	-0.588	-0.463
	p	**<0.001**	-	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**

*Spearman's rank correlation coefficient test

Table 5. Correlation of disease duration, treatment duration, DAS-28 score, HAQ score and Quality of Life subscale scores of patients with RA*

Characteristics		VAS	HAQ	Physical functioning	Role physical	Role emotional	Vitality	Mental health	Social functioning	Bodily pain	General health
Duration of disease (year)	r	0.023	0.325	-0.274	-0.166	-0.183	-0.097	-0.041	-0.129	-0.076	-0.143
	p	0.777	**<0.001**	**<0.001**	**0.040**	**0.023**	0.233	0.614	0.112	0.350	0.078
Duration of disease (year)	r	0.049	0.266	-0.214	-0.151	-0.186	-0.071	-0.013	-0.118	-0.064	-0.068
	p	0.549	**0.001**	**0.008**	0.063	**0.021**	0.384	0.878	0.146	434	401
Das-28 score	r	0.708	327	-0.193	-0.457	-0.129	-0.065	-0.059	-0.233	-0.395	-0.122
	p	**<0.001**	**<0.001**	**0.017**	**<0.001**	0.113	428	471	**0.004**	**<0.001**	0.132

*Spearman's rank correlation coefficient test, RA: Rheumatoid arthritis

exacerbations, chronic inflammation, structural damage, changes in the transmission and perception of pain and pain itself are observed in patients with RA due to the effect of coping mechanisms (27). In our study, pain scores increased as the disease activity of RA increased (r=0,708, p<0,001). Strand et al. (28) stated that patients with RA described any day they spend pain-free as a "good day", emphasizing that this situation was rare. Lisitsyna et al. (29) stressed that the severity of pain in patients with RA was high in those using conventional disease-modifying antirheumatic drugs (DMARDs), and Simon et al. (30) stated that treatments that inhibited the JAK/STAT pathway provided successful pain management. In our study, the treatments of adult and elderly patients with RA were statistically different and antirheumatic treatment was more common in the adult group, whereas steroid, biologic agents and non-steroidal anti-inflammatory drugs were more common in the elderly RA group.

According to the results of the HAQ, the group with less physical limitations in activities of daily living was elderly patients with RA, whereas limitations were more common in elderly non-RA individuals. In our study, it was thought that this was caused by a high number of chronic diseases in elderly non-RA individuals and poor health conditions which required hospitalization and treatment in the internal diseases clinic. As seen in Table 2, although the number of patients with chronic kidney disease, coronary artery disease, diabetes and hypertension were higher in both elderly groups compared to the adult RA group, these diseases were more common in the elderly non-RA group (p<0.05). One of the reasons for the low functionality in elderly individuals without RA may be that geriatric syndromes are very common in the elderly in general. Multiple comorbidities are difficult to manage in elderly patients and this increases susceptibility to geriatric syndromes (31,32) and negatively affects functional capacity (33).

In our study, although the mean RA disease activity scores in both RA groups were similar, the disease activity was moderate in adult patients with RA and mild in elderly patients with RA according to the criteria used to evaluate the DAS-28 scores. In addition, although the number of chronic diseases was higher in the elderly RA group, the level of physical limitations in activities of daily living was higher in adult patients with RA than in the elderly RA patients. The adult RA group was more active in daily life and participated in social and business life more than the elderly RA group. As a matter of fact, in our study, it was seen that adult patients with RA were more active workers than elderly patients with RA, and their functionality worsened as disease activity score increased. It was thought that both this situation and moderate disease activity level may have contributed to the perception that adult patients with RA were more limited in daily activities compared to elderly patients with RA. Moreover, it was predicted in the study that sociodemographic factors might also affect the level of limitation in activities of daily living because the number of patients in the adult RA group who had been giving care to their family members was higher than in the elderly RA group. Independent of the disease, females are generally expected to organize housework and take more responsibility in the care of children and the elderly as well as maintain an active work life. Therefore, expecting fulfilling these duties and responsibilities may lead to the perception of more restriction in activities of daily living due to the effect of rheumatoid arthritis.

When the perceptions of patients regarding quality of life were evaluated, the median scores of the adult patient group on quality of life subscales were higher compared to the other two elderly patient groups. It was found that quality of life decreased as age increased. An increase in the number of chronic diseases in the elderly (34), use of multiple medications, decreased cognitive functions (4), emotional problems (4,35,36), physical inactivity (37), and withdrawal from social life (38) are all factors reducing the quality of life of the elderly group. In our study, similar to the literature, the number of chronic diseases and the number of medications used due to chronic diseases were high and the number of active workers was low in the elderly population.

In the study, it was observed that the level of physical function, one of the subscales of quality of life, in the elderly non-RA patient group was lower than in both RA groups. It was thought that this difference observed especially in the two elderly groups of which mean ages were very close to each other, was due to the fact that the elderly non-RA group had more chronic kidney disease, diabetes, coronary artery disease and that the general condition of these patients was poor and required inpatient treatment, rather than old-age related physiological and psychosocial changes. While susceptibility to geriatric syndromes increases due to the presence of multiple comorbidities, functional capacity decreases (31,33). Geriatric syndromes have been shown to be associated with lower quality of life in several different elderly populations (32,39). In the study, physical role limitations, social functionality, and mental health levels of the elderly non-RA patients were statistically significantly lower than adult patients with RA. Moreover, the social functionality level was better in the elderly patients with RA than in the elderly non-RA patients but their pain, general health status, vitality, and emotional role limitation levels were not statistically different.

As disease activity increases in RA, functional limitation increases. For this reason, it is important to stratify adult and elderly RA groups as remission and low, moderate or high disease activity according to the scores obtained from DAS-28 in order to evaluate the physiological changes and comorbid conditions brought by old age and the effect of RA on functional status. The limitation of our research was that this stratification could not be made.

Study Limitations

The descriptive type of the research prevents the generalization of the results to the population. Research results are based on patients' self-report, which may cause bias in elderly patients' recall of their health status.

Implications

Although the disease activity of elderly patients with RA is lower than adults, these patients have more chronic diseases and have a lower quality of life. For this reason, it is recommended that healthcare professionals evaluate chronic conditions in patients and their quality of life as well as disease activity in elderly patients with RA, and offer individualized health care.

Conclusion

In the study, elderly patients with RA showed a mild disease activity and more chronic diseases than adult patients with RA. Compared to adult patients with RA, elderly patients with RA had fewer physical limitations in activities of daily living and their severity of pain was not different. On the other hand, the physical and social functionality of elderly patients who had received treatment at the hospital due to a chronic disease other than RA were lower, and the quality of life of adults was better compared to the elderly. When these results are considered, it is recommended to consider disease activity, comorbid conditions, physical and psycho-social capacities rather than age in planning the care of patients.

Ethics

Ethics Committee Approval: Eskişehir Osmangazi University, Non-invasive Clinical Research Ethics Committee (date: 15.05.2018/no: 17).

Informed Consent: In the study, patients who met the inclusion criteria were informed by a researcher and written consent was obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: F.U., N.Ş.Y.B., A.Ö., Design: F.U., N.Ş.Y.B., A.Ö., Data Collection or Processing: F.U., N.Ş.Y.B., A.Ö., Analysis or Interpretation: F.U., N.Ş.Y.B., A.Ö., Literature Search: F.U., N.Ş.Y.B., A.Ö., Writing: F.U., N.Ş.Y.B., A.Ö.

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Original Article

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The Relationship between the Hospital Discharging Duration of the Patients Diagnosed with COVID-19 who had Ambulatory and Inpatient Treatment and the Frequency of Their Physical Activity before COVID-19

COVID-19 Teşhisi Konan Ayakta ve Hastanede Yatarak Tedavi Gören Hastaların Hastaneden Taburcu Olma Süresi ile COVID-19 Öncesi Fiziksel Aktivite Sıklığı Arasındaki İlişki

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ABSTRACT

Objective: This study aims to evaluate the correlation between physical activity before pandemic and quarantine measures, hospitalization status and length of stay in patients infected with coronavirus disease-19 (COVID-19).

Methods: A total of 638 people participated in the study. Of the participants 47.8% (n=305) were female and 52.2% (n=333) were male. Chi-square test was used to determine whether or not there was a correlation between hospitalization status and hospitalization duration and other variables.

Results: It was found that there was no significant correlation between rates of hospitalization and gender ($p>0.05$). There was a significant correlation between the frequency of doing physical activity before COVID-19 and hospitalization status among patients diagnosed as having COVID-19 ($p<0.05$). As the number of days of being physically active decreased, the length of hospital stay increased. There was a significant correlation between the frequency of doing physical activity before COVID-19 and the duration of hospitalization in patients diagnosed as having COVID-19 ($p<0.05$). As the number of days of being physically active increased, the length of hospital stay decreased.

ÖZ

Amaç: Bu çalışma, koronavirüs hastalığı-19 (COVID-19) ile enfekte olan hastalarda pandemi ve karantina önlemleri öncesi fiziksel aktivite ile hastaneye yatış durumu ve yatış süresi arasındaki ilişkiyi değerlendirmeyi amaçlamaktadır.

Yöntemler: Araştırmaya toplam 638 kişi katıldı. Katılımcıların %47,8'i (n=305) kadın, %52,2'si (n=333) erkek idi. Hastanede yatış durumu ile hastanede yatış süresi ve diğer değişkenler arasında ilişki olup olmadığını belirlemek için ki-kare testi kullanıldı.

Bulgular: Hastaneye yatış oranları ile cinsiyet arasında anlamlı bir ilişki olmadığı saptandı ($p>0,05$). COVID-19 tanılı hastalarda COVID-19 öncesi fiziksel aktivite sıklığı ile hastanede yatış durumu arasında anlamlı bir ilişki vardı ($p<0,05$). Fiziksel olarak aktif olunan gün sayısı azaldıkça hastanede kalış süresi uzadı. COVID-19 tanılı hastalarda COVID-19 öncesi fiziksel aktivite sıklığı ile hastanede kalış süresi arasında anlamlı bir ilişki bulundu ($p<0,05$). Fiziksel olarak aktif olunan gün sayısı arttıkça hastanede kalış süresi azalmakta idi.

Sonuç: Sonuç olarak, COVID-19 pandemisi öncesinde fiziksel olarak aktif olmak, hastalık nedeniyle hastaneye yatışların

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ABSTRACT

Conclusion: Consequently, being physically active before the COVID-19 pandemic contributes to the prevention of hospitalization due to illness, shortening of hospitalization duration and a milder course of the disease.

Keywords: COVID-19, physical activity frequency, duration of hospitalization

ÖZ

önlenmesine, hastanede yatış süresinin kısalmasına ve hastalığın daha hafif seyretmesine katkı sağlamaktadır.

Anahtar Sözcükler: COVID-19, fiziksel aktivite sıklığı, hastanede yatma süresi

Introduction

Coronvirus disease-19 (COVID-19) has spread rapidly all over the world since the beginning of 2020. More than 531.550.610 million cases of COVID-19 have been reported worldwide and more than 6.302.982 people died as from confirmation of the first case (as of 9 June 2022) (1). In Turkey, the first patient was diagnosed on March 11, 2020, and as of July 12, 2022, the total number of patients was 15,180,444 and the number of deaths was 99,057 (2,3). In addition to the mortality rates associated with COVID-19, some adverse effects on physical and mental health such as increased anxiety, depression or stress during lockdown have been determined (4,5). It has been proven that this novel coronavirus causes severe symptoms of illness among people of all ages, but older adults with multiple morbidities are at highest risk for poor prognosis due to COVID-19 (6). Being physically active, promoting the individual and community health, and contributing to the social, cultural and economic development of all nations enable people to maintain their daily lives in safer and more comfortable environments. For this reason, it is aimed to prevent the increased sedentary lifestyle among adults and adolescents and to achieve a relative decrease of 15% in sedentary lifestyle by 2030 (7). Significant evidence shows that physical inactivity and sedentary behavior increase the risk of many chronic diseases and shorten life expectancy (8). Therefore, it is very important to maintain an active lifestyle at home during the pandemic and not to completely interrupt or change people's lifestyles for the health of the general population, especially for those with risk factors and the elderly. Regular physical activity is one of the most important activities for a healthy life. Regardless of their age, for all individuals, doing regular physical activity is equivalent to maintaining health. It is suggested that moderate physical activity strengthens the immune system compared to sitting (9). As a direct result, decreased physical activity and increased inactivity have been associated with impaired well-being and mental, physical and metabolic health. During the pandemic, surveys aiming to assess the effects of lockdown on inactivity and to reveal insufficient physical activity were conducted in many countries (10,11).

The higher rates of COVID-19-related hospitalizations in people aged 65 and over are a worrying issue regarding public health services and costs. Since the pandemic causes deaths and serious health problems, World Health Organization and country governments have taken a series of measures including isolation and adopting social distancing to prevent the spread of the virus. Along with these measures, behavioral measures such as personal hygiene, wearing a mask, healthy nutrition and physical activity are potential strategies to prevent or alleviate the disease (12,13).

Some studies in the literature suggest that being physically active can alleviate the effects of COVID-19 in humans and reducing or eliminating inactivity will likely result in significant increases in the life expectancy of the world's population (14-16). Another study reported that physical inactivity increased the relative risk for admission in COVID-19 hospital in a UK cohort by 32% (17), suggesting that adopting an active lifestyle might reduce the risk of serious infections. This finding was supported by another population-based study that showed that consistent adherence to PA guidelines was strongly associated with a reduced risk of serious COVID-19 outcomes among infected adults (18). Recently, a retrospective study reported that sedentary lifestyle was associated with mortality in inpatients with COVID-19 [hazard ratio (HR), 5.91] (19).

Additionally, all these studies offered physiological hypotheses that could explain such correlation. Therefore, physical activity may be an important prevention strategy against COVID-19. It may also play a key role in preventing hospitalizations and promoting faster recovery of infected patients. This study aims to evaluate the correlation between physical activity before pandemic and quarantine measures, hospitalization status and length of stay in patients infected with COVID-19. We think that the present study, which will investigate the hypothesis that physically active patients diagnosed as having COVID-19 have a lower time of discharge compared to patients with insufficient physical activity level, will contribute to the literature in this sense.

Methods

Design

This study was carried out upon the approval (decision dated: 18.05.2021 and numbered: 06) of Social and Human Sciences Research Ethics Committee. The study was a cross-sectional study examining the correlation between time of discharge and pre-COVID-19 physical activity levels in outpatients and inpatients diagnosed as having COVID-19. The data were obtained by sending the electronic link of the online (google form) questionnaire to individuals who were diagnosed as having COVID-19 between June and August 2021 and who wanted to participate in the study voluntarily, through social

media, hospital staff, and medical care providers across the country. Seven hundred thirty nine patients to whom the online questionnaire was delivered voluntarily participated in the study within the specified periods. Six hundred thirty eight patients (female and male) who filled out the questionnaire appropriately and completely were included in the study. All participants gave written informed consent online.

Data Collection Tools

In the study, the questionnaire prepared by the researchers reviewing the studies in the literature included questions about participants' personal information (gender, age, height, weight, smoking status, presence of chronic disease), pre-COVID-19 physical activity level, hospitalization status, and discharge times of inpatients (20,21). Patients who were diagnosed as having COVID-19 through polymerase chain reaction (PCR) viral test (qPCR), blood test and rapid antibody test and discharged from the hospital were included in the study. Exclusion criteria for patients were determined as follows; having difficulty in completing the electronic form, being illiterate, being currently hospitalized and having symptoms of COVID-19.

Statistical Analysis

The computer program SPSS version 22 was used for data analysis. Number (n) and percentage (%) values were used in the analysis of demographic variables of the participants. Chi-square test was used to determine whether or not there was a correlation between hospitalization status and hospitalization duration and other variables. Significance level was accepted as $p<0.05$. GraphPad Software The GraphPad Prism 6 was used for graphical expression (Figure 1).

Results

Descriptive statistics of the participants relating to the anthropometric parameters and percent demographic distribution are shown in Table 1 and Figure 2, respectively. A total of 638 patients participated in the study. Of the participants 47.8% (n=305) were female and 52.2% (n=333) were male. Their mean age was 51.86±21.48.

When the rates of hospitalization due to COVID-19 were compared, it was found that there was no significant correlation between rates of hospitalization and gender (X^2 =0.009, $p>0.05$).

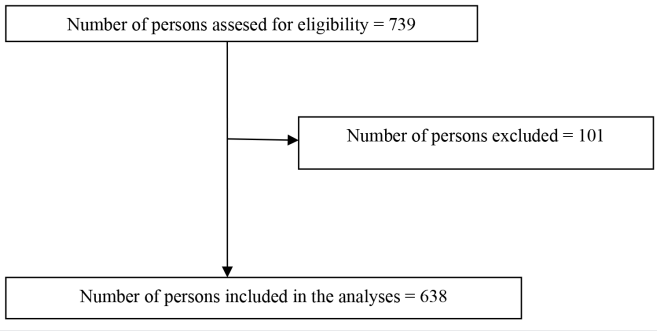

Figure 1. Descriptive statistics of the participants

The rate of hospitalization in patients aged 65 and older was more than twice compared to adults aged 0-45 (X^2 =138.279, $p<0.05$). While 78.7% of the patients who were hospitalized due to COVID-19 were smokers, 62.0% of the outpatients were non-smokers (X^2 =98.988, $p<0.05$). Similarly, it was found that while 81.6% of the inpatients suffered from a chronic disease, 61.8% of the outpatients had no chronic disease (X^2 =107.893, $p<0.05$, Table 2).

It was determined that 71.2% of the inpatients who received treatment due to COVID-19 did not do physical activity and 52.4% did physical activity for 1-3 days. On the other hand, the rate of those who did physical activity for 4-7 days was 12.9%. Of the outpatients 87.1% were physically active for 4-7 days a week. There was a significant correlation between the frequency of doing physical activity before COVID-19 and hospitalization status among patients diagnosed as having COVID-19 (X^2 =81.169, $p<0.05$). Per the results of the current study, the duration of hospitalization is related to the frequency of physical activity levels before COVID-19 to a greater extent (Table 3). In other terms, our results clearly indicated that the individuals who had a decreased physical activity level before COVID-19 had relatively longer stay at the hospital before they were discharged (Figure 4).

When the participants' durations of hospitalization for COVID-19 were compared, it was found that there was no significant correlation between duration of hospitalization and gender (X^2 =0.144, $p>0.05$). In very old patients (85 years and over), the duration of hospitalization was considerably higher (89.4%) compared to the others (X^2 =20.953, $p<0.05$). Among the patients who were hospitalized due to COVID-19, 90.9% of smokers were hospitalized for 8 days or more, and non-smokers were hospitalized less (X^2 =81.971, $p<0.05$). Similarly, 97.2%

Table 1. Descriptive statistics of the participants

	Mean	Standard deviation
Age	51.86	±21.48
Height (cm)	174.15	±7.31
Weight before COVID-19 (kg)	75.35	±10.84
Current weight (kg)	78.06	±10.73

(n=638)
COVID-19: Coronavirus disease-2019

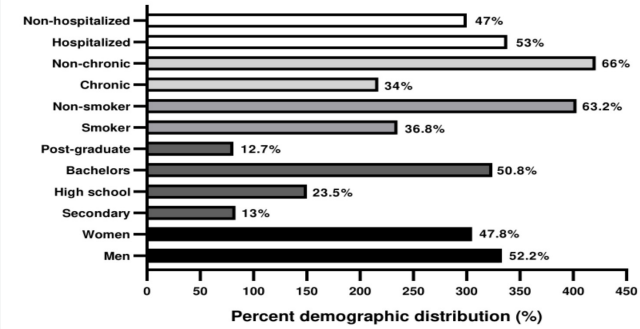

Figure 2. Hospitalization status based on frequency of doing physical activity before COVID-19

of patients with chronic diseases among the inpatients were hospitalized for longer times (X^2 =124.038, p<0.05) (Table 4).

It was determined that among the inpatients who received treatment due to COVID-19, 97.9% of those who did not do physical activity and 52.4% of those who did physical activity for 1-3 days were hospitalized for 8 days and more. On the other hand, 23.5% for those who did physical activity for 4-7 days were hospitalized for 8 days and more. There was a significant correlation between the frequency of doing physical activity before COVID-19 and the duration of hospitalization in patients diagnosed as having COVID-19 (X^2 =93.227, p<0.05). As the

Table 2. Chi-square table of hospitalization based on some variables

		Hospitalization							
		Yes		No		Total		X^2	p
		N	%	N	%	N	%		
Gender	Female	161	52.8	144	47.2	305	100	0.009	0.926
	Male	177	53.2	156	46.8	333	100		
Age	Adolescent (0-17)	11	42.3	15	57.7	26	100	138.279	**0.001***
	Young (18-44)	145	36.3	254	63.7	399	100		
	Young-old (45-74)	61	78.2	17	21.8	78	100		
	Old (75-84)	74	90.2	8	9.8	82	100		
	Very old (85 and over)	47	88.7	6	11.3	53	100		
Smoking	Yes	185	78.7	50	21.3	235	100	98.988	**0.001***
	No	153	38.0	250	62.0	403	100		
Chronic disease	Yes	177	81.6	40	18.4	217	100	107.893	**0.001***
	No	161	38.2	260	61.8	421	100		

*p<0.05; X^2: Pearson chi-square test

Table 3. Chi-square table for hospitalization status based on frequency of physical activity before COVID-19

		Hospitalization status							
		Yes		No		Total		X^2	p
		N	%	N	%	N	%		
FPAB COVID-19	No	141	71.2	57	28.8	198	100	81.169	**0.001***
	1-3 days	186	52.4	169	47.6	355	100		
	4-7 days	11	12.9	74	87.1	85	100		

*p<0.05; FPA: Frequency of physical activity before COVID-19; X^2: Pearson chi-square test

Table 4. Chi-square table for duration of hospitalization based on some variables

		Duration of hospitalization							
		0-7 days		8 days and longer		Total		X^2	p
		N	%	N	%	N	%		
Gender	Female	47	28.8	116	71.2	163	100	0.144	0.705
	Male	58	30.7	131	69.3	189	100		
Age	Adolescent (0-17)	9	75	3	25	12	100	20.953	**0.001***
	Young (18-44)	51	32.3	107	67.7	158	100		
	Young-old (45-74)	20	32.8	41	67.2	61	100		
	Old (75-84)	20	27	54	73	74	100		
	Very old (85 and over)	5	10.6	42	89.4	47	100		
Smoking	Yes	17	9.1	170	90.9	187	100	81.971	**0.001***
	No	88	53.3	77	46.7	165	100		
Chronic disease	Yes	5	2.8	172	97.2	177	100	124.038	**0.001***
	No	100	57.1	75	42.9	175	100		

*p<0.05; X^2: Pearson chi-square test

Table 5. Chi-square table for duration of hospitalization based on frequency of doing physical activity before COVID-19

		Duration of hospitalization							
		0-7 days		8 days and longer		Total		X^2	p
		N	%	N	%	N	%		
FPAB COVID-19	No	3	2.1	138	97.9	141	100	93.227	**0.001***
	1-3 days	89	45.9	105	54.1	194	100		
	4-7 days	13	76.5	4	23.5	141	100		

*p<0.05; X^2: Pearson chi-square test; FPAB: Frequency of physical activity before COVID-19
COVID-19: Coronavirus disease-2019

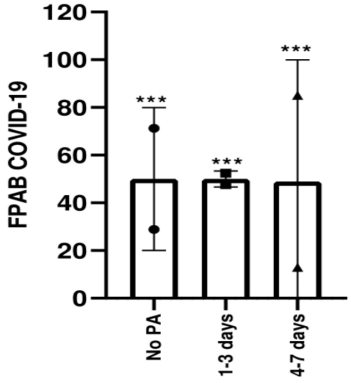

Figure 3. Duration of hospitalization in terms of frequency of doing physical activity before COVID-19
****p<0.05*
COVID-19: Coronavirus disease-2019

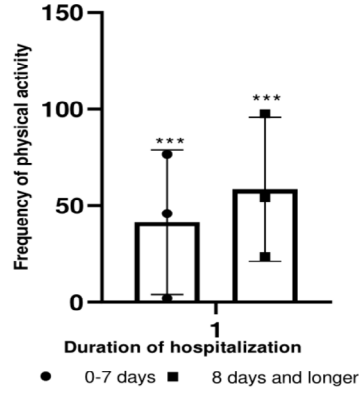

Figure 4. Duration of Hospitalization in Terms of Frequency of Doing Physical Activity Before COVID-19
****p<0.05*
COVID-19: Coronavirus disease-2019

number of days of being physically active increased, the length of hospital stay decreased (Table 5 and Figure 3).

Discussion

The findings of the study revealed no significant correlation between the genders of the participants and their hospitalization status for COVID-19 and duration of hospitalization. It can be asserted that the hospitalization and thus the length of hospital stay are mostly associated with exposure to the virus, immune system, genetic factors, age, chronic disease and similar conditions, regardless of gender. In their study, Turan and Parmaksız (22) included 3506 patients who were hospitalized due to the diagnosis of COVID-19 and stated that hospitalization status and duration of hospitalization did not differ according to the gender of the individuals. The findings obtained from the study are compatible with results of the study. De Souza et al. (23), on the other hand, reported in their study that there was a difference between genders in terms of hospitalization status and the rate of hospitalization was higher in men than women. In the study conducted by Price-Haywood et al. (24) on 3,481 participants, they compared hospitalization and death rates between white and black patients with COVID-19 and found that the hospitalization rates of women were lower than the rates of men. It was thought that the difference between the results of these studies and the result of the present study was associated with the characteristics of the sample group, and the fact that they were conducted in different countries and in different age groups. Furthermore, the fact that men have a higher rate of contracting COVID-19 and being hospitalized than women is associated with the fact that men consume products that adversely affect the immune system, such as alcohol and cigarettes at higher rates (25,26).

While a significant correlation was found between the ages of inpatients diagnosed as having COVID-19, their hospitalization status and hospitalization duration, the rate of inpatient treatment in patients aged 65 and over was more than twice that of adults aged 0-45. Additionally, the duration of hospitalization was higher in very old (85 years and over) patients (89.4%) compared to individuals in the other age groups. As the individuals get older, their number of hospitalizations due to the disease increases and their duration of hospitalization is prolonged. It can be asserted that the elderly have many chronic diseases and their immune systems are weak, which increases the risk of these individuals contracting the disease, and therefore they have the disease more severely. As a matter of fact, in their study, Price-Haywood et al. (24) demonstrated the age variable as a factor affecting the hospitalization status due to COVID-19 and stated that the hospitalized patients had a mean age of 54 years. Likewise, Du et al. (27) stated that individuals aged 65 and over had an alarmingly high rate of COVID-19-related hospitalization and mortality. In another study, it was emphasized that COVID-19 caused less negative effects in individuals under the age of 50, while the effects and mortality rates were higher in older individuals (28,29). The findings of that study and the

results of the present study were similar, which supported the literature regarding the correlation between COVID-19 and age.

The findings of the present study indicated that a great majority of patients who were hospitalized due to COVID-19 smoked and suffered from chronic diseases. Likewise, smokers and those with chronic diseases among inpatients had longer hospital stays. A correlation was found between smoking and having a chronic disease and the hospitalization status for COVID-19 and the length of stay in the hospital. It is known that smoking has negative effects on human health and causes diseases such as chronic obstructive pulmonary disease and asthma. Since COVID-19 is also an upper respiratory tract infection, it is possible to say that individuals who contract the disease and are smokers suffer from the disease more severely when infected. Furthermore, due to the weaker immune systems of individuals with chronic diseases, it is thought that the hospitalization rates and durations of these individuals are higher if they are infected. Numerous studies that are similar to findings of the present study have reported that there is a correlation between smoking and the risk of contracting COVID-19 disease and the severity of the disease (30-33). Sandalcı et al. (34) stated in their review study that individuals with chronic diseases had a higher risk of being infected with COVID-19, the disease progressed more severely in these individuals when infected, and the mortality rate is higher with intensive care. Likewise, there are many studies in the literature reporting that there is a correlation between presence of chronic disease and hospitalization due to COVID-19, and between length of stay and severe course of the illness (29,31,35,36). The results of the other studies and the findings of the present study reveal that both smoking and having a chronic disease are important factors affecting the process of COVID-19.

In the present study, it was determined that there was a significant correlation between the frequency of physical activity before COVID-19 and the hospitalization status and duration of hospitalization among the individuals diagnosed as having the disease. De Souza et al. (23) also reported in their study that physical activity was correlated with hospitalization duration, and doing physical activity at enough level shortened the duration of COVID-19-related hospitalization. The result of that study is compatible with results of the present study. In addition, there are many studies that are consistent with the results of the present study and show that the rates of contracting COVID-19, hospitalization and death rates have reduced in individuals who do physical activity compared to sedentary individuals (19-21,37,38). Although there are many factors associated with COVID-19, it can be said that this situation can be associated with the positive effects of physical activity on the immune system and the fact that physically active individuals have a stronger immune system compared to sedentary ones. These studies suggest that physical activity can prevent poor outcomes in infected patients in terms of COVID-19-related hospital admissions, hospitalization status, and duration of hospitalization. However, in a study, it was stated that there was no significant correlation between the length of stay and physical activity levels of patients hospitalized due to COVID-19 (39). This study differs from the results of the present study and many other studies. It can be said that the difference was caused by the characteristics of the sample group included in the study and the level of the physical activity of the individuals included in the study. Although low and moderate physical activity is beneficial for the immune system, high-intensity activities can suppress the immune system.

Study Limitations

The limited number of studies evaluating the correlation between the hospitalization status and duration of individuals with COVID-19 and the frequency of doing physical activity before COVID-19 constitutes the strength of the present study. While this makes the present study important, it also has limitations. The main limitations of the study are that data were collected by questionnaire instead of a direct measurement method (pedometer, etc.) in determining the frequency and level of physical activity, of the sample was inadequate to represent the population, individuals from different populations were not reached, and the data collection process covered only a few months. In addition, the results of the study should be interpreted due to the existing limitations and the fact that this study is an observational study, the results should be interpreted cautiously.

Conclusion

Consequently, being physically active before the COVID-19 pandemic contributes to the prevention of hospitalization due to illness, shortening of hospitalization duration and a milder course of the disease. Physical activity can be regarded as a tool to protect from negative effects in COVID-19, as in all other diseases. Considering many different factors, PA in inpatients with COVID-19 can be associated with hospital admission, hospitalization and length of stay. Particularly being physically active in preventing COVID-19 may prevent the comorbidity associated with a poor prognosis for this disease. In addition, it can be asserted that physical inactivity is a predictor of longer hospital stays among patients with COVID-19 living in the community. Adequate physical activity is associated with a lower prevalence of COVID-19-related hospitalizations. Therefore, the current data of the present study suggest that being physically active among inpatients with COVID-19 may change the patients' hospital admission, hospitalization status and length of stay.

Ethics

Ethics Committee Approval: This study was carried out upon the approval (decision dated: 18.05.2021 and numbered: 06) of Social and Human Sciences Research Ethics Committee.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: E.G., N.D., P.T.D., Design: E.G., N.D., P.T.D., Data Collection or Processing: E.G., N.D., P.T.D., Analysis or Interpretation: E.G., N.D., P.T.D., G.U., Literature Search: E.G., N.D., P.T.D., Writing: E.G., N.D., P.T.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

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Opinions of Students in the Field of Health on Distance Education During the COVID-19 Pandemic: A Cross-Sectional Study

COVID-19 Pandemi Sürecinde Sağlık Alanında Öğrenim Gören Öğrencilerin Uzaktan Eğitime Yönelik Görüşleri: Kesitsel Bir Çalışma

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ABSTRACT

Objective: It is important to determine the opinions and preferences of students about distance education as its use is becoming more and more prevalent because of the Coronavirus disease-19 (COVID-19) pandemic. It was aimed to determine the opinions of students in the field of health about distance education during the COVID-19 pandemic.

Methods: This was a cross-sectional, descriptive study which was conducted at the Faculty of Health Sciences of a foundation university in İstanbul. The data were obtained from 476 students who were studying at the Faculty of Health Sciences of a university between June and July 2021, using a Student Information Form and Student Opinions on Distance Education Survey.

Results: When asked their opinions on distance education, most described that face-to-face education was more useful than distance education (65.1%) and that having practical lessons with distance education negatively affected their learning (61.1%). Conversely, most of the students expressed that they could listen to the parts of the lessons they did not understand again (93.1%), could listen to the lessons they missed (90.3%), and that distance education provided them with the convenience of taking lessons wherever internet access was available (76.7%).

Conclusion: The results indicated that students did not have considerable problems during distance education, they benefited

ÖZ

Amaç: Koronavirüs hastalığı-19 (COVID-19) pandemisi nedeniyle uzaktan eğitim kullanımı yaygınlaşırken öğrencilerin görüşlerini ve tercihlerini belirlemek önemlidir. Çalışmada, sağlık alanında öğrenim gören öğrencilerin COVID-19 pandemisi sürecinde uzaktan eğitime ilişkin görüşlerinin belirlenmesi amaçlandı.

Yöntemler: Tanımlayıcı ve kesitsel nitelikteki bu çalışmanın verileri Haziran-Temmuz 2021 tarihleri arasında İstanbul'da bir üniversitenin sağlık bilimleri fakültesinde öğrenim gören 476 öğrenciden toplandı. Araştırma verileri, Öğrenci Bilgi Formu ve Öğrencilerin Uzaktan Eğitime Yönelik Görüşlerini Değerlendirme Formu kullanılarak elde edildi.

Bulgular: Öğrencilerin yaş ortalaması 20,62±2,21 idi. Öğrenciler çoğunlukla kadın (%86,8), 2. sınıfta (%33,2) ve hemşirelik ve ebelik bölümlerinde okuyan (%39,9) öğrencilerden oluşmakta idi. Uzaktan eğitimle ilgili görüşleri sorulduğunda, çoğunluğu yüz yüze eğitimin uzaktan eğitimden daha yararlı olduğunu (%65,1) ve uygulamalı derslerin uzaktan eğitim ile yapılmasının öğrenmelerini olumsuz etkilediğini (%61,1) belirtmiştir. Bununla birlikte öğrencilerin büyük bir çoğunluğu derslerde anlamadığı yerleri tekrar dinleyebildiğini (%93,1), katılamadığı dersleri dinleme imkanı bulduğunu (%90,3) ve internet erişiminin olduğu her yerde derslere girebilme kolaylığı sunduğunu (%76,7) ifade etmişlerdir.

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ABSTRACT

from the advantages of distance education and were generally satisfied with it. In relation to the problems experienced during the pandemic, we recommend to take measures especially for applied lessons, to continue to benefit from the advantages of distance education by combining it with formal education in appropriate lessons, and to make necessary improvements by evaluating the opinions of students on a departmental basis.

Keywords: COVID-19, distance education, satisfaction, students

ÖZ

Sonuç: Öğrencilerin uzaktan eğitim sırasında önemli düzeyde problem yaşamadıkları, uzaktan eğitimin avantajlarından yararlandıkları ve uzaktan verilen eğitimden genel olarak memnun oldukları görülmektedir. Bu süreçte yaşanan sorunlarla ilişkili olarak özellikle uygulamalı derslere yönelik önlemlerin alınması, uzaktan eğitimin sadece kriz dönemlerinde uygulanan bir yöntem olarak görülmeyip uygun olan derslerde örgün öğretim ile birleştirilerek avantajlarından yararlanmaya devam edilmesi ve bölüm bazında öğrenci görüşlerinin değerlendirilerek gerekli iyileştirmelerin yapılması önerilir.

Anahtar Sözcükler: COVID-19, uzaktan eğitim, memnuniyet, öğrenciler

Introduction

The Coronavirus disease-19 (COVID-19) pandemic resulted in substantial changes worldwide with its impacts on economy, social life, and education and especially on the health system (1). Countries had to take measures to contain the spread of the virus and to protect public health. The measures taken in education during the pandemic affected all levels of the education system, from pre-school to higher education (1,2). Closing schools to prevent the spread of infectious diseases by breaking the chain of transmission in children and hence in the community is often thought of as an option to contain flu epidemics (3). Indeed, many countries decided to temporarily close schools, universities and other educational institutions during the COVID-19 pandemic (4,5). Academic institutions, like many others, adapted all lectures, meetings and other face-to-face seminars to online teaching to ensure their and students' safety (6,7). They proceeded to develop strategies to explore this new way of teaching, facilitate adaptation to changes, meet new emerging needs, and support educators and students to work with new technologies (8).

Distance education had to be implemented rapidly to manage the process effectively and to prevent students from experiencing problems such as delayed graduation and lost semester, both in our country and worldwide (9,10). Besides providing several advantages such as saving of time and space and the opportunity to review the lessons and reinforce learning, it caused considerable problems for teachers, students and administrators (11,12). Increased costs for schools and universities, weak infrastructure as well as unfamiliar problems such as inadequate digital teaching opportunities surfaced as barriers to this rapid transition. Some personal and professional problems also occurred among students and educators as adapting to the sudden transition to distance education required extra effort (13,14). In particular, the educators had difficulty transferring the lessons in the curriculum they normally gave face-to-face to online format, finding alternative methods for applied lessons, and measuring and evaluating learning (8).

The advent of COVID-19 required schools to be innovative, flexible and respond quickly to maintain the education of students in the field of health because health sciences teaching required an education system based on theory and clinical practice and should support students' cognitive, sensory, and psychomotor skills (8). The target here is therefore not only to acquire clinical skills and theoretical knowledge and but also to advance the acquired skills. Students should develop effective cognitive skills and professional competence, communication, decision-making and teamwork skills they will require as they provide healthcare throughout their professional lives (15). The students trained in health schools must therefore be equipped with expert, qualified and qualified knowledge since healthcare provision will directly affect human health. The measures and initiatives the managers of healthcare institutions will take will be decisive in preventing the current problems from causing negative consequences in the future. Thus, determining the current problems in distance education can provide guidance in making the necessary improvements and revisions. This study was carried out to determine the opinions of students in the field of health about distance education during the COVID-19 pandemic.

Methods

Study Design, Setting and Sample

This descriptive and cross-sectional study was carried out between June and July 2021. The study population covered all students (n=2518) attending classes at the Faculty of Health Sciences of a university in Istanbul. The minimum sample size was calculated as 224, with 95% confidence interval (α=0.05) and p=0.8 for ±5% sampling error. The sample included 476 students who agreed to participate in the study.

Data Collection

The data were collected online by sending the data collection tools to the university e-mail addresses of the students via Google Forms. A letter describing the purpose and scope of the study was also sent to students' e-mail addresses. If willing to participate in

the research, they first gave their consent on the informed consent page and were then provided with access to the data collection tools. Students who answered all questions were considered for the research.

Student Information Form

This form, which was prepared by the researchers in line with the literature (16-18), consisted of 14 questions about the sociodemographic characteristics of students and their experiences with distance education during the pandemic.

Student Opinions on Distance Education Survey

This form was also created by researchers based on the literature information (17,19,20) to determine the opinions of students studying in the field of health on distance education. It included 35 questions in two parts: Negative Opinions on Distance Education (19 questions) and Positive Opinions on Distance Education (16 questions). The questions in the form were answered as "yes", "no" or "partly".

Ethical Considerations

The permission of the COVID-19 Scientific Research Evaluation Commission under the Ministry of Health, General Directorate of Health Services was obtained before starting collecting data. In addition, ethical approval was given by the Biruni University Ethics Committee on 21 May 2021 (decision no: 2021/51-24).

Statistical Analysis

Statistical analysis were performed using the SPSS 23 software package. Descriptive statistics (percentage, mean, standard deviation) were used to evaluate the data, and the chi-square test was used for inter-group comparisons. Statistical significance was set at $p \leq 0.05$.

Results

Their mean age was 20.62±2.21. The majority were female (86.8%) and 2nd year students (33.2%). Of the students 39.9% were studying in nursing and midwifery departments and 83.6% were living with their families (Table 1).

Most of them used computers while attending online lessons (74.4%) and did not have any problems with internet access (55.7%). Of them 34.2% had no difficulty in understanding the theoretical lessons, 46.6% participated in the laboratory lessons face to face, 38.7% did clinical practice and 48.3% had difficulties in understanding practical lessons. Of them 50.6% deemed the means the university offered to access distance education lessons sufficient, most (44.7%) did not want distance education to continue after the pandemic. Students reported that they were generally satisfied (49.1%) that the lessons were taught via distance education (Table 2).

Their negative opinions about distance education were "Face-to-face education is more useful than distance education" (65.1%), "Applied lessons given with distance education negatively affect my learning" (61.1%) and "I think I am more successful in face-to-face training" (55.5%), respectively. Their positive opinions about distance education were "I have the opportunity to listen to the parts that I missed or did not understand during the lessons" (93.1%), "I have the opportunity to listen to the lessons if I miss them." (90.3%) and "I can attend lessons wherever there is internet access" (76.7%), respectively (Table 3).

There was a significant difference between the students' grade and their satisfaction with the distance education provided ($p<0.01$). 1st year students were more satisfied with distance education compared to the 2nd, 3rd and 4th year students. No significant difference was found between the students' age, gender, department, and their satisfaction with distance education ($p>0.05$) (Table 4). There was a significant difference between students' gender and their opinions about the continuation of distance education after the pandemic ($p<0.05$). Male students' opinions were more in favour of continuation of distance education after the pandemic compared to the female students. No significant difference was observed between students' age, grade and department and their views on the continuation of the lessons with distance education ($p>0.05$).

Discussion

Natural disasters, biological problems and wars with their local and global negative impacts on human life have always existed

Table 1. Descriptive characteristics of students (n=476)

	Mean ± SD	Min-max
Age	20.62±2.21	18-43
	n	%
Age group		
18-20 years	269	56.5
21 years and above	207	43.5
Gender		
Female	413	86.8
Male	63	13.2
Grade		
1st year	124	26.1
2nd year	158	33.2
3rd year	127	26.7
4th year	67	14.1
Department		
Nursing/midwifery	185	39.9
Physiotherapy and rehabilitation/ ergotherapy	93	19.5
Child development	99	20.8
Speech and language therapy/audiology	53	11.1
Nutrition and dietetics	46	9.7
Where they lived		
With family	398	83.6
Dormitory	52	10.9
Friend's house	26	5.5

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

throughout history. It is important to make distance education systems more efficient in keeping with the contemporary technological developments, especially to offer new technical progresses for applied lessons, so that educational activities may be sustained should any of these occur. The current pandemic has provided an opportunity in the form of an inevitable experience to identify deficiencies and faults of the distance education system (21).

Having high satisfaction and successful experiences with distance education can contribute to developing a positive attitude towards distance education by enabling learning efficiency (22,23). In our study, students' most positive opinions on the Student Opinions on Distance Education Survey were "I have the opportunity to listen to the parts that I missed or did not understand during the lessons", "I have the opportunity to listen to the lessons if I miss them" and "I can attend lessons wherever there is internet access", respectively. The students also expressed

Table 2. Students' experiences with distance education (n=476)

	n	%
The device you used to take online lessons		
Computer	354	74.4
Smart phone	108	22.7
Tablet	14	2.9
Did you have internet access problems where you lived?		
Yes	62	13.0
No	265	55.7
Partly	149	31.3
Did you have difficulty in understanding the lesson when the theoretical lessons were given by distance education?		
Yes	151	31.7
No	163	34.2
Partly	162	34.0
Did you participate in person in the laboratory practice during the pandemic?		
Yes	222	46.6
No	104	21.8
Partly	41	8.6
I don't have any applied lessons	109	22.9
Did you do clinical practice during the pandemic?		
Yes	184	38.7
No	170	35.7
I don't have a clinical practice lesson	122	25.6
Did you have difficulty in understanding the lesson when the applied lessons were given by distance education?		
Yes	230	48.3
No	118	24.8
Partly	128	26.9
Did you find the opportunities offered by your university to the distance education lessons sufficient?		
Yes	241	50.6
No	77	16.2
Partly	158	33.2
Would you like the distance education to continue after the pandemic?		
Yes	140	29.4
No	213	44.7
Partly	123	25.8
In general, were you happy that the lessons were given by distance education?		
Yes	234	49.1
No	126	26.5
Partly	116	24.4

Table 3. Student Opinions on Distance Education Survey (n=476)

Negative Opinions on Distance Education		Yes		Partly		No	
		n	%	n	%	n	%
1.	I am having system-related problems in accessing and during lessons.	189	39.7	116	24.4	171	35.9
2.	I find it difficult to listen to and understand the lessons.	187	39.3	88	18.5	201	42.2
3.	I don't believe that I have learned the lessons enough.	242	50.8	95	20.0	139	29.2
4.	Applied lessons given with distance education negatively affect my learning.	291	61.1	79	16.6	106	22.3
5.	I think I am more successful in face-to-face training.	264	55.5	138	29.0	74	15.5
6.	I am not happy with the continuation of distance education.	215	45.2	101	21.2	160	33.6
7.	I am having problems reaching the lecturer who is conducting the lesson.	86	18.1	125	26.3	265	55.7
8.	There are some parts that I do not understand due to the limited time of the lesson.	154	32.4	87	18.3	235	49.4
9.	I am having problems following the lessons.	191	40.1	80	16.8	205	43.1
10.	Face-to-face education is more useful than distance education.	310	65.1	104	21.8	62	13.0
11.	I'm having problems because I don't have a computer.	76	16.0	44	9.2	356	74.8
12.	I cannot exchange information about lessons because distance education prevents me from interacting with my friends.	235	49.4	60	12.6	181	38.0
13.	I find it very boring to be in front of the computer all the time.	282	59.2	70	14.7	124	26.1
14.	Distance education prevents me from actively participating in lessons.	236	49.6	57	12.0	183	38.4
15.	I'm having problems accessing resources for the given assignments.	134	28.2	100	21.0	242	50.8
16.	Conducting applied lessons with distance education does not negatively affect my learning.	139	29.2	92	19.3	245	51.5
17.	I am having problems in clinical practice.	131	27.5	168	35.3	177	37.2
18.	Distance education prevents me from being active enough in clinical practice.	211	44.3	128	26.9	137	28.8
19.	I prefer face-to-face exams.	112	23.5	124	26.1	240	50.4
Positive Opinions on Distance Education		**Yes**		**Partly**		**No**	
		n	**%**	**n**	**%**	**n**	**%**
1.	I can view all my lessons live.	313	65.8	76	16.0	87	18.3
2.	I have the opportunity to listen to the lessons if I miss them.	430	90.3	22	4.6	24	5.0
3.	I have the opportunity to listen to the parts that I missed or did not understand during the lessons.	443	93.1	18	3.8	15	3.2
4.	I can listen to my lessons in a comfortable environment at home.	342	71.8	71	14.9	63	13.2
5.	I can attend lessons wherever there is internet access.	365	76.7	43	9.0	68	14.3
6.	Although I have technical problems in accessing the lessons, I can solve the problem immediately by receiving technical support (supportive feedback).	237	49.8	133	27.9	106	22.3
7.	The camera and sound quality have been sufficient in technical terms in the lessons I have viewed.	302	63.4	101	21.2	73	15.3
8.	Thanks to distance education, I do not waste my time.	295	62.0	78	16.4	103	21.6
9.	I can easily communicate with the lecturers of the lessons when necessary.	277	58.2	131	27.5	68	14.3
10.	Distance education is more suitable for me due to the intensity of my lessons.	214	45.0	112	23.5	150	31.5
11.	I think distance education is more effective and efficient than face-to-face education.	112	23.5	124	26.1	240	50.4
12.	I feel more comfortable in the distance education process.	263	55.3	86	18.1	127	26.7
13.	I have improved my knowledge and skills in computer use.	322	67.6	72	15.1	82	17.2
14.	I don't have any problems preparing my assignments.	268	56.3	105	22.1	103	21.6
15.	Distance education is more suitable for me as I have to work part-time.	176	37.0	95	20.0	205	43.1
16.	I find the distance education method more economical.	280	58.8	90	18.9	106	22.3

Table 4. Comparison of students' satisfaction with distance education by their socio-demographics (n=476)

	Satisfaction with distance education							
	Yes		No		Partly			
	n	%	n	%	n	%	Test value U/χ^2	p
Age								
18-20 years	133		63		73		[1]4.129	0.127
21 years and above	101		63		43			
Gender								
Female	196		111		106		[1]4.184	0.123
Male	38		15		10			
Grade								
1st year	78		18		28		[2]19.351	**0.004***
2nd year	73		43		42			
3rd year	50		44		33			
4th year	33		21		13			
Department								
Nursing/midwifery	100		34		51		[2]14.590	0.068
Physiotherapy-ergotherapy	47		31		15			
Child development	47		30		22			
Speech and language, therapy/audiology	22		17		14			
Nutrition	18		14		14			

*p<.01

as positive comments that they improved their knowledge and skills in computer use, were able to save time, found distance education more economical, and had the opportunity to listen to lessons in a comfortable environment at home. The topics in which students expressed the most negative opinions about distance education were "Face-to-face education is more useful than distance education", "Applied lessons given with distance education negatively affect my learning" and "I find it very boring to be in front of the computer all the time", respectively. In a similar study by Dinç and Erdoğan (24) evaluating the opinions of nursing students regarding distance education during the COVID-19 pandemic, the most important problems the students in distance education had were technology-related and technical problems, problems with lessons and exams, and personal problems related to learning types. Students expressed the possibility of re-accessing the lessons as an important advantage and the inability to conduct clinical/laboratory practice and the ineffectiveness of the lessons as the most important disadvantages of distance learning (24).

Students' attitudes towards distance education during the COVID-19 pandemic appeared to be positive in some studies in the literature (17,25-27). Students described it as advantageous given the circumstances caused by the pandemic, but they also believed that the disadvantages of distance education posed a serious problem for educational activities (28,29). Students found distance education advantageous because it was a precaution against the risk of face-to-face education, offered a time-space advantage and provides equal opportunity in education but also considered it disadvantageous because it eliminated the advantages of face-to-face education (effective communication, social environments, obligation to attend lessons, effective learning) and physical conditions were not sufficient (21). The students believed that online learning limited the consequences of social contact, saved money and energy in transportation to university, and provided an easier learning method, but they also mentioned disadvantages such as the need for technical tools, absence of direct contact with the lecturer/staff, difficulty to provide a quiet environment at home while taking online lessons and more absenteeism compared to traditional education (30). The majority of students thought that their social life came to a halt temporarily during the pandemic. They wanted to follow their lessons remotely due to the pandemic but believed that the exams in the distance education system did not help improve their competencies and they did not want distance education to continue under normal conditions (28). The students found distance learning inefficient for practical lessons and efficient for theoretical lessons, and they were not very content with it due to the lack of mutual communication. The lack of question-answer opportunity in distance education and problems in logging into the system caused negative reactions by the students, while positive reactions were about the opportunity to watch lessons again regardless of time and place (29). The problems that nursing students experience in distance education were related to the problems in the distance education infrastructure of the university, lack of face-to-face education, limited opportunities, and the mood and exam anxiety brought about by the pandemic (10). According to Yılmaz et al. (31), laboratory and practice limitations might negatively affect the efficiency of the lessons in transforming theoretical knowledge into skill in clinical practice lessons.

Students' opinions on distance education may depend on several factors such as the technological infrastructure facilities of the institutions, whether lecturers and students can use technology, educator interactions with students, and technical means or problems of the students. The technological infrastructure of the university where the study was conducted was suitable for distance education, which enabled a fast and successful transition to this process. Besides, synchronization of lessons, supportive attitudes of the lecturers and their openness to communication, and the ability of the institution managers to respond rapidly to these problems seemed to facilitate the process and contributed positively to student satisfaction.

In this study, the technological device the students used the most was computers. The studies conducted by Bakhov et al. (16), Kızıltepe and Kurtgöz (18) and Elfirdoussi et al. (32) obtained similar results. Some other studies, on the other hand, reported that smartphones were mostly used for online access during the COVID-19 pandemic (25,33). According to Şener et al. (34), nursing students could be distracted and lessons could be interrupted if they followed lessons with mobile phones, because of the smaller field of view compared to the computer and incoming messages and calls. Therefore, it is clearly important for students to log into online lessons from a computer for effective learning.

In our study, students stated that having practical lessons via distance education caused difficulties in understanding the lesson. The theoretical hours of the applied lessons were fully given online as part of the measures taken during the pandemic, but the students were required be present during clinical practice and laboratory lessons were held face-to-face, although the hours were reduced in many departments to avoid negative consequences. This seemed to have somewhat relieved students' concerns about the application. Almahasees et al. (35) found in their study with faculty members and students that the majority of them preferred face-to-face education. In another study (36), the majority of students preferred the theoretical lessons to be conducted online whenever possible while they described face-to-face lessons as more beneficial in applied lessons. According to studies with nursing students, students regarded distance education methods as insufficient for laboratory and clinical applications, which were important components of nursing education (24,27). The reasons why students favoured face-to-face education included the advantages of instant feedback and more effective communication between students and teachers and the fact that certain skills were acquired in practical training. Although face-to-face education was mostly preferred in previous studies, distance education allowed the continuation of education and theoretical lessons (37). However, it was established during the pandemic that face-to-face education and clinical practices were indispensable in applied sciences. Online learning was implemented as a temporary alternative due to COVID-19 and was unlikely to replace face-to-face learning (35). Still, distance education is seen as a necessity in the age of information and technology with increasing prevalence of digitalization.

According to this study, there was a significant difference between the students' satisfaction with distance education with their grade years. The 1st year students were more satisfied with the distance education compared to 2nd, 3rd and 4th year students. This difference may be explained by the different knowledge level and set of skills that students at each grade level have. Durgun et al. (26) found different results in their study examining students' opinions on distance education where the Student Opinions on Distance Education Survey mean score was the lowest in the 1st and the highest in the 3rd year students, with a statistically significant difference between the mean scores of these two groups. This finding of the study was attributed to the fact that 1st year students had inadequate knowledge in both theoretical and applied lessons and might think that they would not feel competent when they moved to the next grade (26). Another study (38) on the experiences and opinions of higher education students on distance education during the COVID-19 epidemic also reported different results compared to this study: 1st year students found distance education less useful and less interesting than the students in other grade levels. Students in the 3rd and 4th years are more experienced than 1st and 2nd year students and know what is expected of them in terms of learning outcomes. Since 1st year students are at the beginning of a new education, they need to make more efforts to adapt to the learning process. The authors concluded that 1st and 2nd year students might need more support than the 3rd and 4th year students when switching to distance education (38). There were many studies in the literature showing that students' attitudes towards distance education did not differ significantly by their grade level (14,24,39).

In the current study, female and male students differed significantly in their opinions on whether lessons should still be via distance education after the pandemic: male students wanted distance education to continue after the pandemic more than female students. There was, however, no significant difference between students' satisfaction with distance education by age, gender and department variables. The results of the previous studies indicating that gender (14,26,39) and age (14) were not significantly correlated with distance education satisfaction were similar to the results of this study. On the other hand, there were also study results suggesting significant relationships between age (24,40), gender (40-42) and department (43) and student opinions on distance education unlike this study. Comparing students' views on distance education by gender, it was concluded that male students had more positive opinions on distance education (40,41,43). We are in the opinion that the higher level of satisfaction of male students can be explained by their higher technological literacy level than that of female students (42).

Study Limitations

The study was limited to the students who were studying at the faculty where the research was conducted and who agreed to participate in the research. Therefore, the results could not be generalized to the whole population. In addition, these findings were obtained from student self-reports and not all students

were included. The strength of the study was that it included the experiences from the beginning of the changes in the education system to normalization within the scope of the measures taken in the COVID-19 pandemic, and the use of the questionnaire that was prepared by the researchers after the pandemic. Previous related studies generally used data collection tools developed before COVID-19 and the studies were conducted while the pandemic was still ongoing.

Conclusion

Based on the study, the students did not experience significant problems with distance education during the COVID-19 pandemic and benefited from the advantages of distance education. They thought that face-to-face education was more beneficial than distance education during the pandemic, and that having practical lessons with distance education affected their learning negatively. A great majority of the students expressed that they had the opportunity to listen or repeat the lessons if they missed or when there were parts they did not understand, and that they could attend the lessons wherever there was internet access. Half of the participants deemed the means offered by the university for access to lessons sufficient. Most of them had difficulties in understanding the practical lessons with distance education and did not want the lessons to continue with distance education after the pandemic. The students participated more in laboratory lessons than clinical practice in this process. The 1st year students reported the most satisfaction with distance education, while male students wanted to continue distance education more than female students after the pandemic.

It is always important to be prepared for distance education for the sustainability of education. Also, establishing large-scale simulation laboratories for applied lessons, evaluating student opinions on a department basis, and continuing to benefit from the advantages of distance education may be important in increasing the quality of education and student satisfaction. We suggest that further studies be conducted on the students who received education during the pandemic to examine the opinions on the positive and negative aspects of distance education after graduation.

Ethics

Ethics Committee Approval: In addition, ethical approval was given by the Biruni University Ethics Committee on 21 May 2021 (decision no: 2021/51-24).

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: G.K., A.K., N.K.B., Concept: G.K., A.K., N.K.B., Design: G.K., A.K., N.K.B., Data Collection or Processing: G.K., A.K., N.K.B., Analysis or Interpretation: G.K., A.K., N.K.B., Literature Search: G.K., A.K., N.K.B., Writing: G.K., A.K., N.K.B.

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Original Article

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The Effect of Video-assisted Breast Milk and Breastfeeding Training Given to the Mothers of Hospitalized Newborns on the Breastfeeding Self-efficacy Success: A Semi-experimental Study

Hastanede Yatan Yenidoğan Annelerine Verilen Video Destekli Anne Sütü ve Emzirme Öz Yeterlik Eğitiminin ve Emzirme Başarısına Etkisi: Yarı Deneysel Bir Çalışma

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ABSTRACT

Objective: This study was carried out to determine the effect of video-assisted breast milk and breastfeeding training given to the mothers of hospitalized newborns on the breastfeeding self-efficacy and success.

Methods: This was a non-randomized semi-experimental study with a pretest-posttest design including two groups. It was carried out with a total of 84 mothers who met the inclusion criteria including 41 mothers in the experimental group and 43 mothers in the control group. Data were collected by a breastfeeding Charting System and Documentation Tool (LATCH) and Postpartum Breastfeeding Self-Efficacy Scale-Short Form (PBSES-SF). While experimental group was given a video-assisted breastfeeding training together with an educational booklet on breastfeeding, control group was given a training only through an educational booklet on breastfeeding. Descriptive statistics were used in statistical analysis; besides, one-way analysis of variance (ANOVA) was used for the comparison of LATCH and PBSES-SF scores between the groups and paired samples t-test was used for comparisons within groups.

ÖZ

Amaç: Bu araştırma, hastanede yatan yenidoğanların annelerine verilen video destekli anne sütü ve emzirme eğitiminin, emzirme öz yeterlilik ve emzirme başarısı üzerine etkisini belirlemek amacıyla yapılmıştır.

Yöntemler: Araştırma iki gruplu öntest-sontest tasarımda randomize olmayan yarı deneysel bir araştırmadır. Çalışma, araştırmaya alınma kriterlerine uyan girişim grubunda 41 ve kontrol grubunda 43 anne olmak üzere toplam 84 anne ile gerçekleştirildi. Girişim grubuna anne sütü ile beslenme eğitim kitapçığı ile birlikte video destekli emzirme eğitimi verilirken, kontrol grubuna sadece anne sütü ile beslenme eğitim kitapçığı kullanılarak emzirme eğitimi verildi. Veriler LATCH Emzirme Tanılama Ölçüm Aracı (LATCH) ve Postpartum Emzirme Öz yeterlilik Ölçeği-Kısa Şekli (PEÖÖ) ile toplandı. Verilerin değerlendirilmesinde tanımlayıcı istatistikler, gruplar arası PEÖÖ ve LATCH puanları karşılaştırması için tek yönlü varyans analizi (ANOVA) ve gruplar içinde karşılaştırması için eşli örnekler t-testi kullanıldı.

Bulgular: Gruplar arasında ortalama öntest emzirme özyeterlik ve emzirme başarısı puanları benzerdi (p>0,05), fakat video destekli

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ABSTRACT

Results: Mean pretest breastfeeding self-efficacy and breastfeeding success scores were similar between the groups (p>0.05); however, breastfeeding self-efficacy and breastfeeding success scores were found to be higher in the experimental group compared to the control group (p=0.00). Moreover, it was found that mean breastfeeding self-efficacy score following the training in the experimental group was significantly increased compared to the score before the training (p=0.00). A moderate level, positive and significant correlation was found between the differences in the breastfeeding self-efficacy and breastfeeding success scores of the mothers before and after the intervention (r=0.470, p<0.01).

Conclusion: The results of the study revealed that video-assisted breast milk and breastfeeding training was more effective than the routine training given by an educational booklet on breastfeeding in enhancing breastfeeding self-efficacy and success.

Keywords: Breastfeeding, training, self-efficacy, video

ÖZ

emzirme eğitimi sonrası emzirme özyeterlik ve emzirme başarısı puanları girişim grubunda kontrol grubuna göre daha yüksekti (p=0,00). Ayrıca girişim grubunda eğitim sonrası ortalama emzirme özyeterlik puanının, eğitim öncesine göre anlamlı olarak arttığı bulundu (p=0,00). Annelerin emzirme özyeterlik ve emzirme başarısı puanlarındaki girişim öncesi ve sonrası farklılıklar arasında orta düzeyde pozitif anlamlı bir ilişki olduğu saptandı (r=0,470, p<0,01).

Sonuç: Araştırmanın sonuçları, video destekli anne sütü ve emzirme eğitiminin, emzirme öz-yeterliğini ve başarısını artırmada emzirmeye yönelik bir eğitim kitapçığı tarafından verilen rutin eğitime göre daha etkili olduğunu ortaya koymuştur.

Anahtar Sözcükler: Emzirme, eğitim, öz yeterlilik, video

Introduction

Breastfeeding is the most fundamental right of the newborn. Breast milk is not only beneficial for the mother and infant, it also has many benefits for the family, society and economy of the country. As breast milk has many benefits, it is also required for mothers to be informed adequately about breastfeeding, to be supported and to feed their babies accurately for improving breastfeeding success and self-efficacy. It has been known that breastfeeding training and support facilitate initiation to breastfeeding and extend its duration (1,2). You et al. (3) reported that individualized perinatal breastfeeding training given to the expectant mothers with gestational diabetes based on self-efficacy theory showed positive effects on postnatal breastfeeding self-efficacy and breastfeeding rates.

It is important to start breastfeeding education during antenatal period and to continue it also during the postnatal period together with group sessions, home visits and individual support (2,4). Breastfeeding support is different than breastfeeding training; it generally starts during postnatal period and covers breastfeeding support services that may be accessed with psychological, physical and financial support (1,5). Among the healthcare professionals, nurses have a key position in empowering, supporting, consulting and guiding the mother during prenatal and postnatal periods (2,6). The training given to the mother by the nurse has a great impact on the continuation of breastfeeding, prevention of breast complications and successful breast feeding (1,2,7,8) The nurses should encourage the mothers about breastfeeding and they should be knowledgeable about psychosocial effects, challenges met and the ways to resolve them (6,9).

World Health Organization recommends to enrich breastfeeding training with written materials and videos in individual or group sessions (2). It has been indicated that breastfeeding training programs should be supported by using new methods such as web-based instructions, videos and written materials in line with the current technological advances in order to be successful (2,7). Recent studies have shown that videos are used commonly in breastfeeding trainings in developing countries due to its cost-effectiveness (10,11). In this context, we consider that video-assisted training given to the mothers of hospitalized babies will be important to determine their breastfeeding self-efficacy and will provide a source to the future studies that will be conducted with various training methods. Therefore, this study was carried out to determine the effect of video-assisted breast milk and breastfeeding training given to the mothers of the hospitalized newborns on breastfeeding self-efficacy and success.

Hypotheses

Hypothesis 01: Video-assisted breast milk and breastfeeding training given to the mothers of the hospitalized newborns does not affect breastfeeding self-efficacy of the mothers.

Hypothesis 1: Video-assisted breast milk and breastfeeding training given to the mothers of the hospitalized newborns increases breastfeeding self-efficacy of the mothers.

Hypothesis 02: Video-assisted breast milk and breastfeeding training given to the mothers of the hospitalized newborns does not affect breastfeeding success of the mothers.

Hypothesis 2: Video-assisted breast milk and breastfeeding training given to the mothers of the hospitalized newborns increases breastfeeding success of the mothers.

Methods

Study Design

This was a non-randomized, semi-experimental study with a pretest-posttest design including two groups.

Setting and Sample

The universe of the study consisted of mothers whose babies were hospitalized in neonatal intensive care 2nd level unit of a university hospital located in a big city in the northern part of Turkey between 06.01.2021-12.25.2021 and who came to breastfeed their babies. A power analysis was done by using G*Power (v3.1.7) program in order to determine sample size. In the calculations assuming that the assessments made between two independent groups in terms of Breastfeeding Self-Efficacy Scale-Short Form scores would have a great impact (d=0.80), it was determined that each group had to include at least 36 individuals in order to obtain a power of 80% (1-β) at a level of α=0.05. Considering that some losses might occur during the study, it was planned to enroll 44 individuals into each group. Among the mothers who met the inclusion criteria, three in the experimental group (EG) and one in the control group (CG) discontinued and left the study. In this case, the study was completed with 41 mothers in EG and 43 mothers in the CG. Mothers who approved to participate in the study (1), who were healthy (2), who were aged 18 years and older (3), whose babies were hospitalized and found to be suitable for breastfeeding by the neonatologists (4), who were literate (5), who did not have a psychiatric problem (6) and who knew Turkish (7) were included. Those who did not approve to participate (1), who were sick (2), whose babies were not found to be suitable for breastfeeding by the neonatologists (3), who experienced a breast problem that might prevent breastfeeding (4), who had mental, cognitive, psychiatric, auditory and visual problems (5), who were illiterate (6) and who did not know Turkish (7) were excluded from the study.

Data Collection Tools

Data were collected by Demographic Information Form, A Breastfeeding Charting System and Documentation Tool (LATCH) and Postpartum Breastfeeding Self-Efficacy Scale-Short Form (PBSES-SF).

Demographic Information Form: This form was prepared in line with the literature (8,9,11) and consisted of a total of 20 questions including some sociodemographic data (age, education status, income status, employment status, place of residency, family type) and obstetric data (pregnancy planning, number of pregnancies, status of experiencing any health problem during pregnancy, gestational weeks, type of childbirth) regarding the mother, data regarding the newborn (sex, weight) and breastfeeding-related characteristics (status of previous breastfeeding, first postpartum breastfeeding time, current feeding pattern, status of any education and the amount of time she wants to breastfeed).

LATCH Breastfeeding Charting System and Documentation Tool: LATCH Breastfeeding Charting System and Documentation Tool was generated by Jensen et al. (12). The instrument is composed of five assessment criteria [L (Latch on the breast), A (Audible swallowing), T (Type of the nipple), C (Comfort breast/nipple) and H (Hold)]. Each item is scored between 0-2 points. Maximum score that can be obtained from the scale is 10 points. As the score taken from the scale increases, breastfeeding success also increases. Turkish adaptation of the scale was carried out by Yenal and Okumuş (13) and Cronbach alpha value was found as 0.95. In this study, cronbach alpha coefficient was calculated as 0.90.

Postpartum Breastfeeding Self-Efficacy Scale-Short Form: This 33-item scale was developed by Dennis and Faux (14); and it was turned into a short form including 14 items by Dennis (15). The scale assesses how competent mothers feel themselves about breastfeeding. All items included in this 5-likert type scale (1= I am not sure at all, 5= I am always sure) have a positive meaning. Minimum score that can be taken from the scale is 14 and the maximum is 70. Higher scores indicate higher breastfeeding self-efficacy. Turkish adaptation of the scale was conducted by Tokat et al. (16) and Cronbach alpha value was found as 0.86. In this study, cronbach alpha coefficient was calculated as 0.85.

Procedures

The eligibility of the mothers who came to the neonatal intensive care unit to breastfeed their babies was evaluated by the researcher. Necessary information was given to the eligible and volunteer mothers and their written informed consents were taken. There were one experimental (intervention) and one control group in the study. The researcher firstly gave video-assisted breast milk and breastfeeding training to the intervention group. When these trainings were completed, the researcher assigned the other eligible mothers to the control group. Mothers in the control group were just given routine breastfeeding training of the hospital and no other intervention was made. Socio-demographic and obstetric data of the mothers were collected at first by using demographic information form; data regarding the babies were obtained from the infant files by the researcher. Breastfeeding self-efficacy was assessed by Postpartum Breastfeeding Self-Efficacy Scale-Short Form and breastfeeding success levels were assessed by LATCH before (pretest) and after breastfeeding trainings lasting for three days (posttest). Intervention time was limited to three days in this study since mean weekly hospitalization time of the newborns in neonatal intensive care 2nd level unit was 5 days. LATCH form was completed by the researcher through observation. LATCH form was simultaneously completed with the researcher and a nurse with 10 mothers and their babies before starting the study, and the concordance between the observers was evaluated. No significant difference was found between the observers for LATCH scores ($p>0.05$) and thus, LATCH was completed by the observation of one researcher. Mothers and newborns enrolled in the pre-application were not included in the study. All these data were collected in the hospital when the mothers came for breastfeeding and when they were available. Data collected and interventions made were carried out without disturbing routine care, follow-up and breastfeeding process of the newborns.

Intervention group: The mothers in the experimental group were given a breastfeeding training with an educational booklet which was prepared by the training nurse of the relevant hospital and which was used routinely in breast milk training by the nurses in intensive care units for 3 days. During the training,

mothers were allowed to watch a video about breast milk and breastfeeding. In this video which was prepared by the researchers, there were practical information including breastfeeding positions, breast holding style, inititation and maintenance of breastfeeding, breastfeeding duration and frequency and the signs showing that the baby was breastfeeding actively and had adequate milk. The duration of video was 15 minutes. Mothers' feedbacks were taken for the information and skills in the video at three days following the training; and the questions of the mothers were answered.

Control group: The mothers in the control group were given a general breastfeeding training with breastfeeding education booklet which was prepared by the training nurse of the relevant hospital and which was routinely used by the nurses in the neonatal units for breastfeeding training for 3 days; and the questions of the mothers were answered. They underwent routine breastfeeding process and no other intervention was made in this group.

Statistical Analysis

Data were analyzed by using the IBM SPSS v.23 (IBM Corp. Armonk, NY, USA) program. Continuous data were presented with descriptive statistics such as number, percentage, arithmetic mean and standard deviation. Chi-square test, Continuity correction test and Fisher's exact test were used for categorical variables to confirm differences in sociodemographic and obstetric characteristics between the groups. PBSES-SF and LATCH scores were compared between groups by one-way analysis of variance (ANOVA); and comparisons within groups were done by Paired samples t-test. The correlations between PBSES-SF and LATCH scores were evaluated by Pearson correlation test. A value of $p<0.05$ was accepted as statistically significant.

Ethical Considerations

Ethics approval to conduct the study was obtained from the Clinical Research Ethics Committee of a university located in the northern part of Turkey (date: 05/28/2021, no: 2021/239); and was conducted in compliance with the Helsinki Declaration. Additionally, all participants were informed about the purpose of the study before the implementation of data collection form and those, who approved to participate, provided a written informed consent (clinical trials: NCT05221463).

Results

Some sociodemographic characteristics of the mothers participated in the study were given in Table 1. No statistically significant differences were found between the groups in terms of mothers' age, education status, income status, employment status, occupation, place of residency and family type ($p>0.05$). Accordingly, mothers were found to show a homogenous distribution in respect to sociodemographic characteristics.

Some obstetric and newborn-related characteristics of the mothers were given in Table 2. No statistically significant differences were found between the groups in terms of number of pregnancies, pregnancy planning, type of childbirth, birth week, birth weight, postpartum skin-to-skin contact, breastfeeding experience, first postpartum breastfeeding time, sex of the newborn, current feeding pattern of the newborn, status of having breast milk and breastfeeding training, time to consider breastfeeding the baby and weight of the baby in the intensive care ($p>0.05$). Accordingly, obstetric and newborn-related characteristics of the mothers were found to show a homogenous distribution.

The comparisons of mean PBSES-SF and LATCH scores of the mothers between and within the groups were given in Table 3. Mean pretest breastfeeding self-efficacy scores were similar between groups (EG: 45.78±9.44; CG: 49.14±7.68; $p=0.07$); however, breastfeeding self-efficacy scores were found to be higher in experimental group following video-assisted training compared to the control group (EG: 64.59±4.82 versus CG: 58.28±7.19; $p=0.00$). When differences within the groups were examined, mean breastfeeding self-efficacy score in the experimental group was found to be significantly increased in the experimental

Table 1. The distribution of some sociodemographic characteristics of the mothers based on groups

Characteristics		EG (n=41)	CG (n=43)	p value
Age (years)	20-25	4 (9.8)	4 (9.3)	0.74[a]
	26-30	21 (51.2)	19 (44.2)	
	31-35	9 (22.0)	14 (32.6)	
	35 and older	7 (17.1)	6 (14.0)	
Education status	Elementary school	8 (19.5)	9 (20.9)	0.80[a]
	Secondary school	12 (29.3)	9 (20.9)	
	High school	7 (17.1)	10 (23.3)	
	Undergraduate and higher	14 (34.1)	15 (34.9)	
Income status	Income less than expenses	0 (0.0)	2 (4.7)	0.13[a]
	Income equal to the expenses	41 (100.0)	39 (90.7)	
	Income more than expenses	0 (0.0)	2 (4.7)	
Employment status	Employed	8 (19.5)	12 (27.9)	0.51[b]
	Unemployed	33 (80.5)	31 (72.1)	
Occupation	Housewife	33 (80.5)	32 (74.4)	0.70[a]
	Officer	6 (14.6)	7 (16.3)	
	Worker	2 (4.9)	4 (9.3)	
Place of residency	Village	1 (2.4)	2 (4.7)	0.12[a]
	County	22 (53.7)	31 (72.1)	
	City	18 (43.9)	10 (23.3)	
Family type	Core	38 (92.7)	38 (88.4)	0.71[c]
	Large	3 (7.3)	5 (11.6)	

Categorical variables were presented as n (%).
[a]Chi-square test, [b]Continuity correction test, [c]Fisher's exact test

Table 2. The distribution of some obstetric and newborn-related characteristics of the mothers based on groups

Characteristics		EG (n=41)	CG (n=43)	p value
Number of pregnancies	1	18 (43.9)	11 (25.6)	0.12[b]
	2 and more	23 (56.1)	32 (74.4)	
Pregnancy planning	Planned	35 (85.4)	30 (69.8)	0.14[b]
	Unplanned	6 (14.6)	13 (30.2)	
Type of childbirth	Vaginal	5 (12.2)	6 (14.0)	1.00[b]
	Cesarean section	36 (87.8)	37 (86.0)	
Birth week	37 and below	22 (53.7)	21 (48.8)	0.82[b]
	38-41	19 (46.3)	22 (51.2)	
Birth weight	2,499 gr and less	9 (22.0)	15 (34.9)	0.41[a]
	2,500-3,500 gr	27 (65.9)	23 (53.5)	
	3,501-4,499 gr	5 (12.2)	5 (11.6)	
Postpartum skin-to-skin contact	Yes	8 (19.5)	9 (20.9)	1.00[b]
	No	33 (80.5)	34 (79.1)	
Breastfeeding experience	Yes	17 (41.5)	20 (46.5)	0.80[b]
	No	24 (58.5)	23 (53.5)	
First postpartum breastfeeding time	Within 60 minutes	8 (19.5)	6 (14.0)	0.55[a]
	After 1 hour	13 (31.7)	11 (25.6)	
	After 24 hours	20 (48.8)	26 (60.5)	
Sex of the baby	Female	17 (41.5)	21 (48.8)	0.64[b]
	Male	24 (58.5)	22 (51.2)	
Current feeding pattern of the newborn	Breast milk	7 (17.1)	6 (14.0)	0.92[b]
	Breast milk and formula	34 (82.9)	37 (86.0)	
Status of education on breast milk and breastfeeding	Yes	27 (65.9)	30 (69.8)	0.88[b]
	None	14 (34.1)	13 (30.2)	
Time to consider breastfeeding the baby	First 6 months	1 (2.4)	1 (2.3)	0.86[a]
	6-12 months	1 (2.4)	2 (4.7)	
	12-24 months	39 (95.1)	40 (93.0)	
Weight of the baby in intensive care		2791.71±625.65	2776.86±632.760	0.91[c]

Categorical variables are presented as n (%).
[a]Chi-square test, [b]Continuity correction test, [c]Independent sample t-test

group following the training (p=0.00). The increase in the mean breastfeeding self-efficacy score in the experimental group (18.80) was significantly higher than the increase in the control group (9.13) (p=0.00). Mean pretest breastfeeding success scores were also comparable between the groups (EG: 3.66±1.97; CG: 4.14±2.34; p=0.31); but, breastfeeding success scores following video-assisted training in the experimental group were found to be significantly higher than the control group (EG: 9.07±1.38 versus CG: 6.67±2.06; p=0.00). Moreover, mean breastfeeding success score following the training in the experimental group was significantly increased compared to the score before the training (p=0.00). The increase in the breastfeeding success score in the experimental group (5.41) was significantly more than the increase observed in the control group (2.53) (p=0.00). Based on these data, it was determined that video-assisted breast milk and breastfeeding training was more effective than the breastfeeding training routinely given in the hospital in enhancing breastfeeding self-efficacy and success levels.

Table 3. The comparison of mean PBSES-SF and LATCH scores between and within the groups

	EG (n=41)	CG (n=43)	Between groups p-value[a]
PBSES-SF			
Pre-test	45.78±9.44	49.14±7.68	0.07
Post-test	64.59±4.82	58.28±7.19	**0.00**
Within group p-value[b]	**0.00**	**0.00**	
Difference	18.80±6.76	9.13±6.39	**0.00**
LATCH			
Pre-test	3.66±1.97	4.14±2.34	0.31
Post-test	9.07±1.38	6.67±2.06	**0.00**
Within group p-value[b]	**0.00**	**0.00**	
Difference	5.41±2.23	2.53±1.96	**0.00**

Data were presented as mean ± SD. [a]One-way analysis of variance (ANOVA), [b]Paired samples t-test.
SD: Standard deviation

Moreover, a positive and significant correlation was found between total breastfeeding self-efficacy and breastfeeding success scores before and after the intervention at a moderate level ($r=0.470$, $p<0.01$). Accordingly, breastfeeding success increased as breastfeeding self-efficacy level of the mothers increased.

Discussion

There is a huge effort made on the breastfeeding of babies in our country and mothers need a significant support on this issue (4,9,17,18). Nurses have an important role and responsibility in providing this support. In this study, it was determined that both routine briefing and video-assisted breast milk and breastfeeding training were effective in improving breastfeeding self-efficacy and success levels. Previous studies have reported that training and breastfeeding consulting provided to expectant mothers before childbirth and to the mothers during postpartum period positively affect breastfeeding initiation time, breastfeeding rate and breastfeeding duration (2,9,17-19).

In the study, video-assisted breast milk and breastfeeding training was determined to be more effective than the verbal training given through an educational booklet on breastfeeding in promoting breastfeeding success as well as breastfeeding self-efficacy. In many studies, it was determined that breastfeeding consulting trainings given in the hospital during early postpartum period were carried out verbally as face-to-face, online and through phone and visual training materials such as brochures (2,7,8,19,20). Video-assisted breastfeeding training given during pregnancy in our country has been determined to be effective in enhancing breastfeeding success and self-efficacy of the mothers (4,17). In the study by Tokat and Okumuş (21), it was found that methods used together with videos in the breastfeeding training given to the mothers in the study group such as slides, models, role-play, peer and case discussions affected breastfeeding self-efficacy perception of the group in a more positive way compared to the control group. Moreover, Mizrak et al. (4) found in their study that breastfeeding training given to the expectant mothers during prenatal period through methods including slides, models and videos promoted breastfeeding self-efficacy and success of the mothers at postpartum first and eighth weeks. Again, in some postpartum studies, video-assisted breastfeeding consulting was found to be effective in gaining knowledge as well as gaining attitudes and behaviors (11,22). In their study, Aditya et al. (22) stated that video-assisted breast milk consulting training helped mothers to understand the procedure and the process better and enhanced their knowledge levels and breastfeeding motivation about baby feding. A study, which was conducted in Malasia, found that videos about breastfeeding aided mothers to change their attitudes towards breastfeeding. In the same study, educators stated that video-assisted breastfeeding training supported mothers in presenting important issues (23). In addition, videos which were prepared for health education in Africa were found to be effective in developing knowledge and positive attitudes for mother and child health among the rural semi-literate communities (10). In the web-based education which was provided by Nicholson et al. (24) for the pregnant women with gestational diabetes, some animation videos on breastfeeding were displayed and 75% of postpartum mothers were found to feed their babies only with breast milk. As different from these, it was reported in another study that making pregnant women in low-income populations to watch educational videos on breastfeeding, prenatal diet and exercise during the third trimester did not affect postpartum hospitalization time, breastfeeding initiation rates and breastfeeding duration (11).

In the current study, it was also determined that breastfeeding success increased as breastfeeding self-efficacy level of the mothers increased. Similarly in the previous studies, a positive and weak/moderate correlation was found between mean LATCH scores and mean breastfeeding self-efficacy scores of the mothers during postpartum period and it was also observed that breastfeeding success increased as their breastfeeding self-efficacy perception increased (25,26). Kılcı and Çoban (27) stated that breastfeeding success at early postpartum period enhanced breastfeeding self-efficacy perception at late postpartum period. In addition, Gökçeoğlu and Küçükoğlu (28) found in their study that mothers perceived their breast milk as more sufficient as their breastfeeding self-efficacy levels increased. Besides, breastfeeding self-efficacy was indicated to be the main potential postpartum assessment tool in the hospital to determine mothers at risk of premature weaning (29).

Study Limitations

There were some limitations of this study. First of all, the results could not be generalized to all mothers of hospitalized newborns since it was a single-center study. Secondly, long-term efficiency of the intervention was not evaluated since no follow-up was made during breastfeeding period.

Conclusion

The results of the study revealed that video-assisted breast milk and breastfeeding training was more effective than the routine training given by an educational booklet on breastfeeding in enhancing breastfeeding self-efficacy and success. Moreover, breastfeeding success of the mothers increased as their breastfeeding self-efficacy level increased.

In order to enhance the efficiency of educational programs on breastfeeding, it is crucial to use new methods in line with the current technological advances such as videos besides written materials. Breastfeeding training and support should be continued together with home visits during postnatal period starting from pregnancy period at healthcare institutions. Besides, it is recommended to conduct other quantitative studies with two or three groups using different training materials and methods together as well as qualitative studies that may determine the quality of training and the opinions and suggestions of the mothers on this issue.

Ethics

Ethics Committee Approval: Ethics approval to conduct the study was obtained from the Clinical Research Ethics Committee of a university located in the northern part of Turkey (date:

05/28/2021, no: 2021/239); and was conducted in compliance with the Helsinki Declaration.

Informed Consent: Additionally, all participants were informed about the purpose of the study before the implementation of data collection form and those, who approved to participate, provided a written informed consent (clinical trials: NCT05221463).

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Authorship Contributions

Surgical and Medical Practices: Ş.Ç., Concept: E.T.B., N.B., Ş.Ç., Design: E.T.B., N.B., Ş.Ç., Data Collection or Processing: Ş.Ç., Analysis or Interpretation: E.T.B., N.B., Literature Search: E.T.B., N.B., Ş.Ç., Writing: E.T.B., N.B., Ş.Ç.

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Original Article

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Parent Skill Assessment Scale (Age 1-3) (PASKAS 1-3): Validity and Reliability Study

Ebeveyn Beceri Değerlendirme Ölçeği (1-3 Yaş): Geçerlik ve Güvenirlik Çalışması

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ABSTRACT

Objective: This study was planned for the development, validity and reliability of the parent skill assessment scale (aged 1-3) (PASKAS 1-3) in order to evaluate the skills of parents with children aged 1-3 in nurturing.

Methods: This study was carried out with a total of 400 parents with children aged 1-3 between September-October in 2022. The validity of the parent skill assessment scale (aged 1-3) (PASKAS 1-3) was tested with content validity and construct validity. Test-retest, Cronbach Alpha reliability coefficient and Item Total Score Correlation coefficient were examined to determine the scale reliability.

Results: The content validity index of the data was between 0.81 and Explanatory factor analysis (EFA) and confirmatory factor analysis (CFA) fit indexes of the scale, which consisted of 3 factors with a total of 30 items, were found as χ2/df: 1.687, RMSEA: 0.041, comparative fit index: 0.87, incremental fit index: 0.87, GFI: 0.90 and Tucker-Lewis index: 0.86. The Cronbach alpha reliability value was 0.82, the test-retest correlation coefficient was 0.74, and the item-total score correlation coefficient was above 0.20.

Conclusion: The scale is a valid and reliable measurement tool that can be used to evaluate child nurturing skills of parents with children aged 1-3 from physical, cognitive, language development and social-emotional aspects.

Keywords: Child, parenting, parents, reliability and validity

ÖZ

Amaç: Bu çalışma 1-3 yaş döneminde çocuğu olan ebeveynlerin çocuk yetiştirmede kendi becerilerini değerlendirmeleri amacıyla geliştirilen ebeveynlik becerilerini değerlendirme ölçeğinin geliştirilmesi, geçerlik ve güvenirliğinin yapılması amacıyla planlanmıştır.

Yöntemler: Araştırma metodolojik yöntem kullanılarak tasarlanmış geçerlik ve güvenirlik çalışmasıdır. Çalışma, Eylül-Ekim 2022 tarihleri arasında 1-3 yaş arasında çocuğu olan 400 ebeveyne uygulanmıştır. Ebeveynlik Beceri Değerlendirme Ölçeğinin geçerliği, kapsam geçerliği ve yapı geçerliği ile test edilmiştir. Ölçeğin güvenirliğini belirlemek için test tekrar test, Cronbach Alpha güvenirlik kat sayısı, Madde Toplam Puan Korelasyon katsayısına bakılmıştır.

Bulgular: Verilerin kapsam geçerlik indeksi 0,81 ile 1 arasında idi. Açıklayıcı faktör analizi (AFA) ile 30 maddelik 3 alt boyuttan oluşan ölçeğin doğrulayıcı faktör analizi (DFA) uyum indeksleri χ2/df: 1,687, RMSEA: 0,04, karşılaştırmalı uyum indeksi: 0,87, artan uyum indeksi: 0,87, GFI: 0,90 ve Tucker-Lewis indeksi: 0,86 olarak bulunmuştur. Ölçeğin Cronbach alpha güvenilirlik değeri 0,82, Test-tekrar test kolerasyon katsayısı 0,74 Madde-Toplam Puan Korelasyon Katsayısı ise 0,20'nin üstünde bulunmuştur.

Sonuç: Ölçek 1-3 yaş döneminde çocuğu olan ebeveynlerin çocuklarını fiziksel, bilişsel, dil gelişimi ve sosyal-duygusal yönden yetiştirme konusunda becerilerinin değerlendirilmesinde kullanılabilecek geçerli ve güvenilir bir ölçektir.

Anahtar Sözcükler: Çocuk, ebeveynlik, ebeveynler, güvenirlik ve geçerlik

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Introduction

The play period in children (1-3 years) is a period in which rapid changes occur in growth and development. During this period, the child's sense of independence and autonomy comes to the fore, while the child's curiosity and interest increase. In this period, besides physical growth changes, cognitive, social-emotional and linguistic developments occur in children (1). Interventions in this period will affect the cognitive development, psychosocial behaviors and personality of the child in the following years (2).

Parents should be able to balance the needs of their children (toilet training, language development, etc.) with the need for autonomy (3). They should be able to provide sensitive care in a way that adapts to their children's cues, emotions, interests and abilities (4). During this period, parents can improve the skills and efforts of the child trying to be autonomous by displaying encouraging attitudes towards them (5). Therefore, parents should be empowered to develop their attitudes and behaviors as their children shift from infancy to play period. Parents may have different attitudes and skills when it comes to raising children. Especially in this period, when physical, cognitive, social, emotional and language development needs are demanding, it is important for parents to feel competent in raising children (6). When children's physical skills, cognitive, language and social-emotional development are supported in the 1-3-year-old period, they can become self-confident and solution-oriented individuals able to make decisions later in adulthood. That's why it's important for parents to develop their parenting skills (4,7).

The literature review shows that the measurement tools that parents can evaluate themselves about child nurturing are generally suitable for children aged 3-6 (8-10). Valid and reliable tools are not available in which parents can evaluate their child-rearing skills specific to the 1-3-year-old age group. For this reason, there is a need for a valid and reliable measurement tool for parents who have children aged 1-3 years to evaluate their own child-rearing skills (11). Besides parents, nurses playing an important role in health assessments and training can use such an assessment tool, thus, nurses can evaluate the child-rearing skills of parents with children aged 1-3 and provide the necessary support to parents.

Objective: This study was planned for the development, validity and reliability of the parenting skill assessment scale, which was developed for parents with children aged 1-3 to evaluate their own parenting skills in terms of children's physical, cognitive, language and social-emotional development.

Methods

Study Design

The study was designed as a methodological research.

Place and time of the research: This online study was carried out between September 14 and October 14, 2022.

Population and sample selection: The population consisted of parents with children aged 1-3 living in different provinces of Turkey. Snowball sampling method, a non-probability and purposeful sampling method was implemented in the study. In the snowball sampling method, any person included in the study population was contacted through social media accounts, and other participants were reached with the help of the contact person. Snowball sampling method was used in order to achieve maximum diversity in the sample. Since the research was a validity and reliability study, it was planned to reach at least 180 parents, 5-10 times the number of items (12). Four hundred parents participated in the study within the specified period.

Inclusion criteria

- Children aged 12-36 months

Exclusion criteria

- Being a non-parent caregiver
- Having child with a chronic illness

Data Collection

The design of the forms was created on Google Forms. The data were collected online through "Parent and Child Descriptive Data Form" and "Parent Skill Assessment Form". The parent and child descriptive data form consisted of 7 questions about age and education level of parents, child age, child gender and number of children) (13-16).

Forming the Data Collection Tool

The parent skill assessment form was created by the researchers in line with the literature (16-20). This form was developed to evaluate the parenting skills of parents with children aged 1-3. A pool of 34 items was created in the draft scale and 11 individuals (7 academic nurses working in the field of child health and diseases, 2 child development specialists, 2 pediatric specialists in the field of child health and diseases) were counselled for expert opinion. It is recommended to seek for at least three expert opinions to determine the content validity of a scale (12,21). Expert opinions were evaluated in accordance with Davis Technique.

The 36-item draft scale, prepared upon expert opinion, was applied to 10 parents to evaluate its intelligibility. Since no changes were made on the draft scale for its intelligibility, the validity and reliability analysis of the forms were started.

Parent Skill Assessment Scale (Age 1-3) (PASKAS 1-3): The number of items in the first scale was 34. Upon the expert opinion, the number of items increased to 36. The number of items decreased to 30 based on the validity and reliability analyzes after the parents filled out the 36-item scale. As a result, the parenting skill assessment scale consisted of a total of 30 items. In the scale, 0 point was scored as "Never", 1 point as "Rarely", 2 points as "Sometimes", 3 points as "Often" and 4 points as "Always". The minimum score that could be obtained from the scale was 0, and the highest score was 120. Lower total score indicated that there was a need for development for parenting skills, and a higher one indicated that the specified parenting skills were appropriate.

Statistical Analysis

The descriptive characteristics of the participants were expressed as number, percentage, minimum, maximum, mean and standard deviation. The SPSS 26.0 (Statistical Software) was used for data analysis and exploratory factor analysis (EFA), and IBM SPSS Amos 16.0 (Analysis of Moment Structures) was used for confirmatory factor analysis (CFA).

Scale content validity was evaluated using the Davis technique. In order to evaluate the construct validity, (EFA) and (CFA) were performed. The Kaiser-Meyer-Olkin (KMO) and Bartlett's test were decided if the scale was suitable for performing EFA and CFA. The scale reliability was evaluated using Cronbach Alpha reliability coefficient, Item-Total Score Correlation Coefficient and Test-Retest analysis.

Ethical Considerations

In the study, written permission was obtained from Gazi University Ethics Commission (with the meeting numbered 15 on September 13, 2022, numbered: E-77082166-604.01.02-455039). In addition, a statement was written for the parents that the information to be obtained would be kept confidential and they could withdraw from the research at any time, and an article confirming that they agreed to participate in the research was placed in the form created on Google forms.

Results

Descriptive characteristics of parents and their children were as follows: three hundred and thirty mothers and 70 fathers participated in the study. The mean age of the mothers was 33.55±4.54 [minimum (min): 20-maximum (max): 53 years], the average age of the fathers was 36.22±5.27 (min: 26-max: 56 years), and the average age of children was 25.01±6.85 (min: 12-max: 36 months). Regarding the educational level of parents, it was found that 61% of the mothers and 58.3% of the fathers had bachelor's degrees. Of the children 43.8% were girls and 56.3% were boys. It was determined that 57.5% of the parents had one child, 34.8% two children, and 7.8% three or more children (Table 1).

Validity Analyzes

Content Validity

Thirty four items were created in the item pool and consulted for expert opinion. Items were evaluated by experts using the Davis technique. Based on expert opinions, the item "I can understand my child peeing in the toilet and pooping on his diaper (I3)" was removed. The expressions "I play with my child every day at the times I set" (I13) and "I paint with my child every day at the hours I set" (I14) were combined as "I do activities such as plays and painting with my child every day, considering the needs of my child". Based on the suggestions from the experts, the following items were added: "I give my child the opportunity to complete his/her own sentence", "I offer options to increase my child's decision-making skills", "I act consistently against the behaviors I want to develop in my child", and "I ignore certain behaviors of my child if they do not harm him/her".

The content validity index (CVI) of the items was checked after the expert evaluation. Based on expert opinions, 34 items were put into final form and the scale was finalized with 36 items. The CVI of the scale was found to be between 0.81-1.

Item analysis: Items with item total score correlation below 0.20 were removed from the draft scale (I3 and I35) (21,22).

Construct Validity

The KMO, Bartlett's test, (EFA) and (CFA) were used for the construct validity of the scale. As a result of the analysis, the KMO value was determined as 0.84, and p=0.001 for the Barlett's test. Since the KMO value was above 0.50 (9,23), EFA was initiated. In the EFA, three factors with an eigenvalue above 1 and explaining 31.5% of the total variance were determined. Based on EFA, items with a factor load of less than 0.30 (24) (I7, I12, I21, I31) were removed from the scale. Eighteen items in Factor 1 (I10, I13, I14, I16, I18, I17, I21, I22, I23, I24, I25, I26, I28, I30, I32, I33, I34, I36), 7 items in Factor 2 (I1, I2, I4, I6, I8, I9, I29) and 5 items in Factor 3 (I5, I11, I15, I19, I20) produced a factor load of more than 0.30 (Table 2).

The CFA was measured if the scale had three factors. When modifications were made between the items of the scale four times, the fit indices were found as $\chi 2/df$: 1.687, RMR: 0.03 The Root Mean Square Error of Approximation (RMSEA): 0.04, The goodness of fit index (GFI): 0.90, comparative fit index (CFI): 0.87, Tucker-Lewis index (TLI): 0.86, incremental fit index (IFI): 0.87 (25) (Table 3) (Figure 1).

Table 1. Descriptive characteristics of parents and their children

Descriptive characteristics	Min	Max	
Maternal age	20	53	33.55±4.54
Paternal age	26	56	36.22±5.27
Child age (months)	12	36	25.01±6.85
	Number (n)	Percent (%)	
Gender			
Girl	175	43.8	
Boy	225	56.2	
Mother's education			
Primary or high school	68	17.0	
Undergradute or postgraduate	332	83.0	
Father's education			
Primary or high school	89	22.3	
Undergradute or postgraduate	311	77.7	
Number of children			
One	230	57.5	
Two	139	34.8	
≥ three	31	7.7	

Min: Minimum, Max: Maximum

Reliability Analyzes

For the reliability analysis, the stability and internal consistency of the scale were evaluated.

Stability: The scale was reapplied to 30 people with an interval of 2 weeks in order to determine the scale stability (26). For the analysis of the test, test-retest was performed and the correlation coefficient was checked. As a result of the analysis, the correlation coefficient was found to be 0.74.

Internal consistency: In the study, the Cronbach alpha value of the 30-item scale was determined as 0.82. The Cronbach's alpha value of the factors was found to be 0.83 for factor 1, 0.63 for factor 2 and 0.60 for factor 3. The item total correlation coefficient was found to be over 0.20 (Table 4). Accordingly, it was determined that the scale was a reliable measurement tool.

Table 2. Factor loads of the scale, eigenvalues in factor loads and percentage of variance explained

Factors	Items	Factor loads	Eigen values	Variance explained
Factor 1	I23	.625	5.948	16.441
	I28	.615		
	I17	.613		
	I14	.608		
	I33	.605		
	I26	.587		
	I21	.564		
	I13	.556		
	I34	.551		
	I32	.519		
	I25	.463		
	I18	.448		
	I24	.430		
	I10	.400		
	I16	.396		
	I22	.343		
	I30	.335		
	I36	.331		
Factor 2	I8	.695	1.852	8.210
	I9	.661		
	I4	.602		
	I29	.446		
	I6	.439		
	I2	.415		
	I1	.327		
Factor 3	I11	.685	1.670	6.916
	I5	.645		
	I19	.571		
	I20	.523		
	I15	.461		
Percent of the total variance: 31.5%				

Table 3. Good fit indices

	X^2/df	RMSEA	GFI	CFI	IFI	TLI
Desired good fit value	≤3	≤0.10	≥0.90	≥0.80	≥0.80	≥0.80
Results	1.687	0.041	0.90	0.87	0.87	0.86

X^2/df: Corrected chi-square, RMSEA: Root mean square error of approximation, GFI = goodness-of-fit index, CFI: Comparative fit index, IFI: Incremental Fit Index, TLI: Tucker-Lewis index

Discussion

In the study, the validity and reliability of the "Parent Skill Assessment Form" was conducted in parents with children aged 1-3 in order to identify their skills according to the developmental characteristics of their children. As a result of the findings obtained from the scale, it was concluded that it was a valid and reliable scale. The form was a 30-item scale that could be filled out by parents.

In order for a measurement tool to produce appropriate data, it must be valid and reliable. Validity and reliability are the two most important criteria used in the evaluation of a measurement tool. The first stage of validity methods is content validity and item analysis.

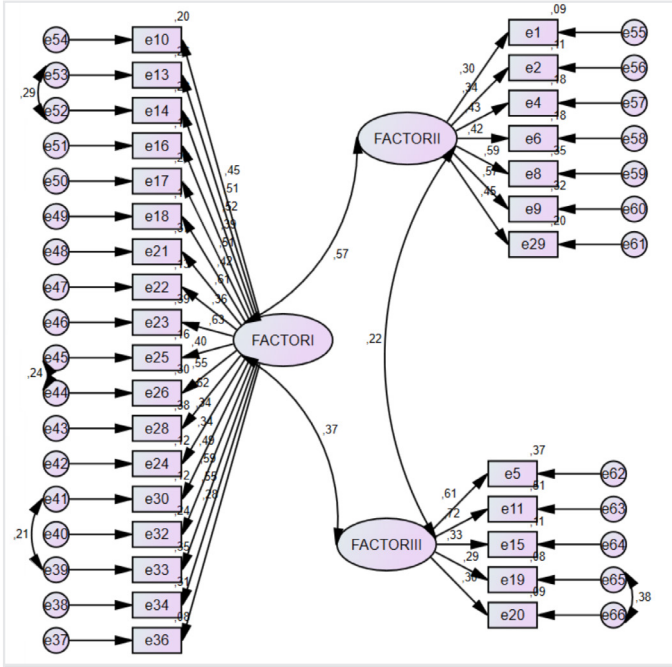

Figure 1. PATH diagram of the scale

Table 4. Cronbach alpha values of the scale

Cronbach alpha 0.82
Factor 1 Cronbach alpha 0.83
Factor 2 Cronbach alpha 0.63
Factor 3 Cronbach alpha 0.60

Content validity should cover the whole quality that a measurement tool aims to measure (23,25,27,28). Items with a CVI above 0.80 are considered appropriate in terms of content validity (23,25,28). In our study, the 34-item draft scale was submitted to expert opinion and the draft scale was rearranged using the Davis technique in line with expert opinions. The 36-item new version of the draft scale was formed after the experts evaluated the 34-item draft according to the Davis technique. In this study, the CVI was found between 0.81 and 1.00 according to the Davis technique, which indicated appropriate content validity (12).

Item analysis was performed to determine the discriminatory power of the scale. Items below 0.20 represent weak correlation with the item total score correlation of the scale (21,22). Therefore, items below 0.20 were excluded from the draft scale (I3 and I35). Thus, the draft scale had 34 items prior to the exploratory factor analysis.

The second stage of validity methods is construct validity. Construct validity is achieved to evaluate the extent to which a scale measures the construct it aims to measure (26). In construct validity, exploratory and CFA is mostly used. In exploratory factor analysis, KMO is used to measure sample adequacy, and Bartlett's test is used to evaluate homogeneity of variances (9,23). Factor analysis is recommended for the scale if KMO >0.50 and Bartlett test p<0.005, (9,23). In our study, the KMO value was 0.84, and p=0.001 for Barlett's test. Therefore, it was concluded that the sample size was sufficient and the variances were homogeneous, and EFA was started. In exploratory factor analysis, factor load value is required to be above 0.30 (24). In our study, at the end of the exploratory factor analysis, 4 items with a factor load of less than 0.3 were removed from the scale. The scale was restructured as 30 items.

Upon the exploratory factor analysis, CFA is performed and the fit indices of the scale are examined. Different acceptable values are presented in the literature for fit indices in CFA Wong et al. (29) considers $\chi 2/df$ of <2-5 to be a good fit, a RMESEA value of 0.06 to be a close fit and a RMESEA value of 0 to be a perfect fit. If the GFI and CFI values are ≥0.90, it indicates the minimum acceptable value, if ≥0.95 it is a good fit, and a value close to 1 indicates a perfect fit, while Gomez and Stavropoulos (30) accept that RMSEA values of 0.06 or less are good fit, 0.07 to 0.08 moderate fit, 0.08 to 0.10 as marginal fit and a value >0.10 as weak fit. Values close to 0.95 for CFI and TLI indicate good fit, values 0.90-0.95 as acceptable fit, and values less than 0.90 as weak fit. In the study of Kalkan and Karadağ (31), the values of fit indices $\chi 2/d$ <3; 0< RMSEA <0.05; 0.95≤ IFI ≤1; 0.95≤ CFI ≤1 and 0.95≤ GFI ≤1indicate perfect fit, and 3<$\chi 2/d$ <5; 0.05< RMSEA <0.08; 0.90≤ IFI ≤0.95; 0.90≤ CFI ≤0.95 and 0.90≤ GFI ≤0.95 indicate acceptable fit. Weerasekara et al. (25) determined the fit indices as reference $\chi 2/df$ ≤3.0, RMR ≤0.05, RMSEA ≤0.10, NFI ≥0.80, GFI ≥0.90, TLI ≥0.80 and CFI ≥0.80. In our study, by making four modifications between the items, the fit indices of the scale were found as $\chi 2/df$: 1.687, RMR: 0.03, RMSEA: 0.04, IFI: 0.87, GFI: 0.90, CFI: 0.87, TLI: 0.86, and they were found to be in appropriate values for the fit indices.

The reliability of a measurement tool is evaluated by its ability to produce consistent and stable results (26). The criteria used in reliability studies are stability and internal consistency. In order to measure the stability of the scale, it is requested to repeat the measurements in at least 15 and at most 30 days (26). For the stability acceptance of the scale, a value of at least 0.70 is taken as a reference (32,33). In our study, the measurements were repeated with an interval of two weeks. For the analysis of the test, the test-retest method was used and the correlation coefficient was checked by Pearson correlation analysis. As a result of the analysis, the correlation coefficient was found to be 0.74. This shows that our scale is not affected by time and measures the structure it aims to measure with the same stability (26). If the responses to the items in a measurement tool are compatible with the total test score, it is stated that the test has internal consistency. The methods used to evaluate the internal consistency are the Kuder-Richardson (KR-20 and KR-21) method and the Cronbach alpha reliability method which is one of the most frequently used reliability criteria in likert type scales (24). In order for the measurement tool to be considered reliable, the Cronbach alpha reliability coefficient should be between 0.60 and 1.00 (31). According to the assessment criteria of Cronbach's alpha coefficient, "the scale is highly reliable" if the coefficient is between 0.80 and 1.00, "the scale is fairly reliable" if it is between 0.60-0.79, "the scale has low reliability" if it is between 0.40-0.59, "the scale is not reliable" if it is between 0, 00-0.39 (31). In our study, the total Cronbach's alpha reliability coefficient of the scale was found to be 0.82, and it was concluded that it was highly reliable. The total item correlation of the scale was found to be over 0.20.

Study Limitations

Due to the online conduct of the study, unreachable parents who did not use social media constituted the limitation of the study.

Conclusion

The scale, developed based on the findings obtained as a result of the reliability and validity study, consists of 30 items and three sub-scales. The scale is scored over the total score. Sub-scales are not scored separately. It was concluded that the scale is a valid and reliable scale that can be used by parents with children aged 1-3 years to evaluate their own child-rearing skills. The scale can be used by nurses, physicians, psychologists and teachers who work with parents who have children between the ages of 1-3.

Ethics

Ethics Committee Approval: In the study, written permission was obtained from Gazi University Ethics Commission (with the meeting numbered 15 on September 13, 2022, numbered: E-77082166-604.01.02-455039).

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Ç., E.K.T., Concept: A.Ç., E.K.T., Design: A.Ç., E.K.T., Data Collection or Processing: A.Ç., E.K.T., Analysis or Interpretation: A.Ç., E.K.T., Literature Search: A.Ç., E.K.T., Writing: A.Ç., E.K.T.

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Original Article

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Psychological Stress and chronic disease management During the COVID-19 Pandemic in Turkey: A Cross-sectional Web-based Study

Türkiye'de COVID-19 Salgını Sırasında Psikolojik Stres ve Kronik Hastalık Yönetimi: Web Tabanlı Kesitsel Çalışma

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ABSTRACT

Objective: To determine the levels of chronic disease management and psychological stress in the era of pandemic, and to evaluate the relationship between them.

Methods: In this cross-sectional study, the sample consisted of 233 patients with chronic diseases. The data were collected with Personal Information Form, the Coronavirus disease-19 (COVID-19) Related Psychological Distress scale (CORPD) and the Patient Assessment of Chronic Illness Care (PACIC) between April 05 and September 30, 2021. The data were collected online via Google Forms and analyzed using number, percent, standard deviation, mode, mean, median, Spearman's correlation, Kruskal-Wallis, Mann-Whitney U, post-hoc multiple comparisons.

Results: The mean CORPD score of the participants was 41.87±10.12, and the mean PACIC score was 63.36±19.26. Male participants with high school degrees, with low-income and health perception and with respiratory diseases had significantly higher mean PACIC score. Female participants with high school degrees, with low-income perception and with cardiovascular diseases had significantly higher CORPD score ($p<0.05$).

Conclusion: Research results showed that moderate psychological stress and suspicion had a positive and stimulating effect on patients' chronic disease management. It is recommended to evaluate the long-term effects of psychological stress, and its impact on chronic disease management in further research.

ÖZ

Amaç: Pandemi döneminde kronik hastalık yönetimi ve psikolojik stres düzeylerini belirlemek ve aralarındaki ilişkiyi değerlendirmektir.

Yöntemler: Kesitsel tipteki bu çalışmanın örneklemini kronik hastalığı olan 233 hasta oluşturdu. Veriler 05 Nisan-30 Eylül 2021 tarihleri arasında Kişisel Bilgi Formu, Koronavirüs hastalığı-19 (COVID-19) ile İlişkili Psikolojik Sıkıntı Ölçeği ve Kronik Hastalık Bakımını Değerlendirme Ölçeği ile toplandı. Veriler, Google Forms aracılığıyla çevrimiçi olarak toplandı ve sayı, yüzde, standart sapma, mod, ortalama, medyan, Spearman korelasyonu, Kruskal-Wallis, Mann-Whitney U, post-hoc çoklu karşılaştırmalar kullanılarak analiz edildi.

Bulgular: Katılımcıların ortalama COVID-19 İlişkili Psikolojik Sıkıntı Ölçeği puanı 41,87±10,12, Kronik Hastalık Bakımını Hasta Değerlendirmesi Ölçeği puanı 63,36±19,26 idi. Lise mezunu, gelir ve sağlık algısı kötü, solunum yolu hastalığı olan, erkek katılımcıların Kronik Hastalık Bakımını Hasta Değerlendirmesi Ölçeği puan ortalamaları anlamlı olarak daha yüksekti. Lise mezunu, gelir algısı kötü, kardiyovasküler hastalığı olan, kadın katılımcılarda COVID-19 İlişkili Psikolojik Sıkıntı Ölçeği puanı anlamlı olarak daha yüksekti ($p<0,05$).

Sonuç: Araştırma sonuçları, orta düzeyde psikolojik stres ve şüphenin, hastaların kronik hastalık yönetimi üzerinde olumlu ve uyarıcı bir etkiye sahip olduğunu göstermiştir. İleri araştırmalarda

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ABSTRACT

Keywords: COVID-19, pandemics, psychological stress, disease management, chronic diseases

ÖZ

psikolojik stresin uzun vadeli etkilerinin ve kronik hastalık yönetimi üzerindeki etkisinin değerlendirilmesi önerilir.

Anahtar Sözcükler: COVID-19, pandemi, psikolojik stres, hastalık yönetimi, kronik hastalık

Introduction

The coronavirus disease-2019 (COVID-19) emerged in December 2019. Globally, there were approximately 6.7 million deaths and it reached over 101.4 thousand deaths in Turkey (1). While emergency health care applications were increased to prevent the spread of coronavirus all over the world, routine services (screening, monitoring, access to health care providers and essential medications, diagnosis, etc.) were disrupted, which changed the priority and delivery of health services (2-7). Hospitals have reorganized their medical and surgical activities since the onset of the pandemic. They have had to suspend non-urgent procedures and surgeries, postpone scheduled treatments and patient transfers, place restrictions on visiting patients and face-to-face consultations. Although these measures have reduced the workloads of hospitals, they have increased the burden of disease in the long term. During this period, a significant increase was observed in cardiovascular complications, and admissions to the emergency department (2-6). In addition, since the start of the pandemic, mortality due to heart failure has tripled, while hospitalization rates have decreased by 40-50% (2). In addition to routine health services during the pandemic, serious changes due to curfews and quarantines have occurred in all areas of life, such as decreased physical activity, sleep problems, smoking and alcohol use, obesity, higher psychological stress. It is reported that all these changes will bring along the burden of chronic disease, psychological and economic problems in the long term, in addition to the risk of COVID-19 (2-4,7-9).

Millions of people have experienced fear, anxiety, and panic because of the COVID-19 and preventive measures, such as lockdowns, curfews, social isolation, restrictions, etc. They have also suffered personal and economic losses since the beginning of the pandemic. However, the pandemic has been particularly detrimental to patients with chronic diseases as they end up experiencing chronic stress, anxiety, depression, etc. (2,7-11). Stress causes gastrointestinal disorders and cardiovascular diseases (12). Too much pandemic related psychological stress makes people more vulnerable to chronic diseases. For this reason, it is extremely important for health professionals to consider mental risks in the prevention and management of diseases (8). Moreover, they should evaluate the psychological stress levels of patients with different chronic diseases and encourage them to manage their diseases (13).

The study had two objectives: (a) determining the levels of chronic disease management and psychological stress in the era of pandemic and (b) evaluating the relationship between psychological stress and chronic disease management. These results will contribute to the literature and encourage healthcare professionals to monitor the psychological stress levels of patients with chronic diseases and manage their conditions. The main research questions were as follows:

(1) What were the psychological stress and chronic disease management levels of participants during the COVID-19 pandemic?

(2) Was there any significant connection between sociodemographic variables and the COVID-19 Related Psychological Distress Scale (CORPD) and the Patient Assessment of Chronic Illness Care (PACIC) scores?

(3) Was there any correlation between CORPD and PACIC scores?

Methods

Study Design

A cross-sectional design was used for this study.

Participants

The study population consisted of all voluntary adult patients with at least one chronic disease for more than six months, and living in Turkey. Considering that the burden of chronic diseases in Turkey is 15.6 million (14) and the total population is 83.61 million (15), it is seen that the incidence of chronic diseases is 18.6%. In this direction, using the online sample calculation tool (www.calculator.net), it was calculated that the minimum number of people to be sampled (with 95% confidence level, 5% tolerance and 80% power) was 233. Participants (n=233) were selected by snowball sampling. The inclusion criteria of the study were:

- Being over 18 years old,
- Having at least one chronic disease for more than six months,
- Being literate,
- Agreeing to participate in the study,
- Having no visual, auditory, or cognitive problems.

After being informed about the research, those who agreed to participate started filling out the scales by clicking the "Agreed" button in the web-based survey.

Data Collection

The data were collected online via a web-based survey software (Google Forms) between April 05 and September 30. Each participant took 10-15 minutes to complete the collection forms. Each participant filled out the data collection forms only once.

Measures

The Personal Information Form, CORPD, and PACIC were used in the measurements.

The Personal Information Form: It was a 20-item form created by researchers to collect sociodemographic (age, education, marital status, etc.) and health information (chronic diseases, medications, etc.).

The COVID-19 Related Psychological Distress Scale (CORPD): It consists of two subscales (1-suspicion and 2- anxiety and fear) and 12 items (16). The scale, adapted into Turkish by Ay et al. (11), is used to measure the level of psychological stress in people who are not infected with COVID-19. The total scores of the five-points Likert-type scale range from 12 to 60. As the score increases, the severity of the psychological stress increases. The Cronbach's alpha of the scale in Turkish was 0.88 (11). Cronbach's alpha values of the total scale (0.93), suspicion subscale (0.89), and anxiety-fear subscale (0.90) were high in this study.

The Patient Assessment of Chronic Illness Care Scale (PACIC): It consists of 20 items and five subscales (1- patient activation, 2- delivery system design, 3- goal setting, 4- problem-solving, and 5- follow-up/coordination) (17). The scale, adapted into Turkish by İncirkuş and Nahcivan (18), assesses the extent patients report receiving care within the past six months. High scores on this 5-point Likert-type scale indicate that individuals with chronic disease are satisfied with their received care and that chronic disease management is sufficient. The Cronbach's alpha of Turkish scale was 0.91 (18). Cronbach's alpha values of the total scale (0.83), goal-setting subscale (0.85), patient activation subscale (0.85), problem-solving subscale (0.89), delivery system design subscale (0.81), and follow-up/coordination subscale (0.89) were high in this study.

Ethical Approval

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The scientific research ethics committee approval was obtained (no: 09/17, date: 12.04.2021).

Statistical Analysis

The data were analysed using number, percent, standard deviation, mode, mean, median (Q1-Q3), minimum-maximum for descriptive data; The Kolmogorov-Smirnov test for normality testing, Spearman's correlation, Kruskal-Wallis, Mann-Whitney U, post-hoc multiple comparisons, and Cronbach's alpha. All analyses were performed in the Statistical Package for Social Sciences (SPSS, Version 21.0 Armonk, NY: IBM Corp.), and significance level was accepted as $p<0.05$.

Results

Participants had a mean age of 41.61±14.62 years. Most of the participants were married (66.5%), female (82%), employed (55.4%), had university degrees (54.5%), had a moderate perception for income (61.4%) and health (52.2%). Eighteen participants had been hospitalized during the pandemic (7.7%), primarily due to cardiovascular diseases (51.6%) (Table 1).

Participants had a mean CORPD score of 41.87±10.12 and the PACIC score of 63.36±19.26, indicating moderate levels of psychological stress and disease management (Table 2).

The CORPD scores significantly differed by gender, education, income, and chronic disease ($p<0.05$). Participants with cardiovascular diseases had a significantly higher CORPD score than those with thyroid disorders. Participants with high school degrees, with a low-income perception and female participants had a significantly higher CORPD score ($p<0.05$) (Table 3).

The PACIC scores significantly differed by gender, education, income, type of chronic disease, and perceived health ($p<0.05$). Participants with a good income, bad health perception, high school degrees and male participants had higher PACIC scores. Scale scores of those with respiratory disease were higher than those with cardiovascular disease (Table 3).

Table 1. Descriptive characteristics of the participants

Variables		n (%)
Gender	Male	42 (18.00)
	Female	191 (82.00)
Marital status	Married	155 (66.5)
	Single	78 (33.5)
Education	Primary	34 (14.6)
	Middle	4 (1.7)
	High	37 (15.9)
	University	127 (54.5)
	Graduate	31 (13.3)
Perceived income	Bad	14 (6.0)
	Moderate	143 (61.4)
	Good	76 (32.6)
Working status	Yes	129 (55.4)
	No	104 (44.6)
Type of chronic disease	Cardiovascular	120 (51.6)
	Endocrine	21 (9.0)
	Respiratory	33 (14.2)
	Thyroid	25 (10.7)
	Cancer	5 (2.1)
	Other (psychiatric etc.)	29 (12.4)
Perceived health	Bad	25 (10.7)
	Moderate	124 (53.2)
	Good	84 (36.1)
Hospitalization	Yes	18 (7.7)
	No	215 (92.3)

The PACIC "patient activation" subscale score was positively correlated with CORPD total and "suspicion" subscale scores ($p<0.05$). The CORPD "suspicion" subscale score was positively correlated with PACIC "follow-up/coordination" and "problem-solving" subscale scores (Table 4). There was a positive correlation between age and CORPD scores ($p<0.05$) (Table 5).

Discussion

Patiens with chronic diseases had difficulty accessing healthcare services, continuing follow-up and treatments, and obtaining medical supplies and essential medications since the onset of the pandemic (2-7). The pandemic has also made patients with chronic diseases more vulnerable to physical and mental problems such as stress, anxiety, depression, and sleep problems (19). Horesh et al. (20) reported that patients with chronic

Table 2. Medians, mods, means of scales and sub-scales

Scales and sub-scales	Median (Q1-Q3)	Mode	Mean ± SD	Minimum-maximum
CORPD total	43.00 (38.00-49.00)	43.00	41.87±10.12	12-60
Anxiety and fear	21.00 (19.00-24.00)	25.00	20.61±4.75	5-25
Suspicion	25.00 (22.00-30.00)	24.00	24.51±6.96	7-35
PACIC total	66.00 (48.50-78.00)	70.00	63.36±19.26	20-100
Patient activation	11.00 (8.00-12.00)	12.00	10.22±3.13	3-15
Delivery system design	10.00 (9.00-12.00)	12.00	10.19±3.14	3-15
Goal setting	16.00 (10.00-19.00)	10.00	15.12±5.28	5-25
Problem solving	14.00 (8.50-16.00)	8.00	13.24±4.56	4-20
Follow-up/coordination	16.00 (10.00-19.00)	17.00	14.57±5.76	5-25

CORPD: COVID-19 Related Psychological Distress Scale, PACIC: Patient Assessment of Chronic Illness Care, SD: Standard deviation

Table 3. Comparison of the descriptive characteristics of the participants with the CORPD and PACIC scores

Variables		CORPD median (Q1-Q3)	U/X^2; p	PACIC median (Q1-Q3)	U/X^2; p
Gender	Male	37.00 (21.00-47.25)	2522.5; 0.001[a]	74.50 (70.00-81.00)	2313.5; 0.001[a]
	Female	43.00 (39.00-49.00)		62.00 (46.00-75.00)	
Marital status	Married	43.00 (39.00-50.00)	5189.50; 0.078[a]	69.00 (48.00-76.00)	5946.00; 0.838[a]
	Single	43.00 (36.00-47.00)		65.00 (49.00-79.25)	
Education	Primary	40.00 (34.25-44.00)	16.570; 0.002[b]	56.00 (48.00-71.00)	25.270; 0.001[b]
	Middle	41.00 (41.00-41.00)		39.00 (39.00-39.00)	
	High	46.00 (43.00-49.00)		75.00 (62.00-80.00)	
	University	43.00 (37.00-52.00)		65.00 (49.00-79.00)	
	Graduate	42.00 (36.00-43.00)		54.00 (40.00-78.00)	
Perceived income	Bad	49.00 (30.00-52.00)	14.917; 0.001[b]	79.00 (68.25-100.00)	7.971; 0.019[b]
	Moderate	43.00 (39.00-51.00)		64.00 (46.00-77.00)	
	Good	42.00 (32.00-46.00)		66.00 (49.00-78.00)	
Working status	Yes	43.00 (37.00-48.50)	5841.0; 0.089[a]	65.00 (48.00-82.00)	5811.50; 0.079[a]
	No	45.00 (38.00-50.00)		66.50 (56.00-72.50)	
Type of chronic disease	Cardiovascular	48.00 (39.00-53.25)	17859.0; 0.007[b]	80.00 (49.00-92.00)	19.431; 0.003[b]
	Endocrine	42.00 (39.00-43.50)		69.00 (57.50-78.00)	
	Respiratory	43.00 (37.00-51.00)		58.00 (37.00-65.00)	
	Thyroid	36.00 (16.00-48.00)		56.00 (38.00-74.00)	
	Cancer	49.00 (39.00-49.00)		52.00 (52.00-83.00)	
	Other (psychiatric etc.)	42.00 (37.50-45.50)		65.00 (50.00-69.50)	
Perceived health	Bad	44.00 (39.00-48.00)	0.114; 0.944[b]	80.00 (67.00-83.00)	14.308; 0.004[b]
	Moderate	43.00 (38.00-49.75)		59.00 (48.00-71.00)	
	Good	43.00 (33.00-49.00)		70.00 (47.50-78.00)	
Hospitalization	Yes	47.00 (41.00-47.00)	1968.00; 0.904[a]	75.00 (49.25-81.25)	2159.00; 0.415[a]
	No	43.00 (38.00-49.00)		65.00 (48.00-78.00)	

CORPD: COVID-19 Related Psychological Distress Scale, PACIC: Patient Assessment of Chronic Illness Care, [a]Mann-Whitney U test, [b]Kruskal-Wallis test

Table 4. The Spearman's correlations between CORPD and PACIC total and sub-scales

Scales and sub-scales	1	2	3	4	5	6	7	8
1. CORPD total	1							
2. Anxiety and fear	0.852*	1						
3. Suspicion	0.945*	0.687*	1					
4. PACIC total	0.062	-0.033	0.107	1				
5. Patient activation	0.184*	0.110	0.181*	0.769*	1			
6. Delivery system design	0.014	-0.036	0.020	0.796*	0.621*	1		
7. Goal setting	-0.027	-0.097	0.028	0.905*	0.605*	0.789*	1	
8. Problem solving	0.096	0.000	0.167*	0.905*	0.651*	0.632*	0.778*	1
9. Follow-up/coordination	0.095	-0.035	0.142*	0.879*	0.577*	0.579*	0.713*	0.790*

*p<0.05, PACIC: Patient Assessment of Chronic Illness Care, CORPD: COVID-19 Related Psychological Distress Scale

Table 5. The Spearman's correlations between age and CORPD and PACIC total

	Age	
Scales	r	p
CORPD total	0.201	0.002
PACIC total	0.040	0.543

CORPD: COVID-19 Related Psychological Distress Scale, PACIC: Patient Assessment of Chronic Illness Care

diseases had lower quality of life and higher levels of anxiety than those without chronic diseases. A meta-analysis of 288,830 participants from 19 countries showed that having mental or physical disorders was associated with a higher prevalence of anxiety and depression in era of the pandemic (21). Considering the one out of every three people experienced psychological stress in era of the pandemic, this study examined the disease management and psychological stress levels of those with chronic diseases during the pandemic (21,22).

In our study, the participants' levels of psychological stress associated with COVID-19 were moderate. The CORPD scores significantly differed by age, gender, education, perceived income, and chronic disease in the study. Older and female participants with high school degrees, low-income perception, and cardiovascular diseases had significantly higher COVID-related psychological stress levels. Gómez-Salgado et al. (23) and Horesh et al. (20) found that people of lower middle age had higher psychological stress levels in the era of COVID-19. Qiu et al. (24) determined that elders had higher psychological stress than children. COVID-19 is having a greater impact on people with chronic illness. Shevlin et al. (25) found that anxiety and depression were also predicted by low income, and pre-existing health conditions in self and others, and specific anxiety about COVID-19 was greater in older participants. Older people with chronic illness are thought to have more psychological stress for three reasons: First, they are more affected by the physiological effects of COVID-19, resulting in increased mortality. Second, they experience more fear in the era of the pandemic because they have chronic diseases. Third, they are bombarded by bad news about COVID-19 on social media platforms (20,23,24). Similar to other studies female participants had significantly higher CORPD scores than males in this study (24,26,27). It is considered that females are more affected in the post-pandemic period in terms of doing most household chores and being pushed out of the workforce, and it is resulting in higher levels of psychological stress. Studies have emphasized that there is a relationship between education levels and anxiety levels during the pandemic period (28-30). Fornili et al. (28) reported a negative correlation between psychological stress and education. However, Salari et al. (29) found that during the COVID-19 pandemic, people with higher levels of education had greater levels of anxiety and stress. Our study found that participants who were high school graduates had higher CORPD scores than participants who were primary school graduates. It is thought that this result may be because highly educated people search for excessive information on social networks and follow the news of the pandemic more closely, resulting in more fear, helplessness, anxiety, and stress. The CORPD scores significantly differed by economic status in the study. Participants with a badly perceived income had higher CORPD scores and psychological stress than those with a good income. Breslau et al. (31) stated that people who were vulnerable to the economic effects of the pandemic should be regarded as a high-risk group for psychological stress. Agberotimi et al. (32) stated that the socioeconomic status of individuals during the pandemic period had serious effects on their mental well-being. Fornili et al. (28) detected a negative correlation between income and psychological stress. In this case, it can be said that the data are similar to the literature. Among patients with COVID-19, there is a high prevalence of cardiovascular disease (33). Participants with cardiovascular diseases had a significantly higher CORPD score. Similarly, McLachlan and Gale (34) reported that high psychological stress exacerbated cardiovascular diseases. Lim, Lim et al. (35) determined that the pandemic made people with cardiovascular diseases more vulnerable to mental problems.

The participants' levels of disease management were moderate in this study. The participants with high school degrees, with a low-income, with a bad health perception, and male participants had a significantly higher mean PACIC score. It was seen that similar results were obtained in other studies evaluating chronic disease management. In the study of Ballering et al. (36), although there was no difference in the prevalence of chronic diseases between

the genders, it was reported that the risk of chronic disease and the burden of somatic symptoms was higher in women. Hazazi and Wilson (37) found that there was no difference in terms of PACIC score between the genders, while scale scores were higher in those with higher education and income. Another study stated that the evaluation of chronic disease care decreased as the quality of life, perception of care and social status got worse (38). It was also stated that PACIC scores were significantly higher in males and patients with high school or higher education due to their socioeconomic advantage (39). When comparisons between diseases were examined, participants with chronic respiratory disease (asthma, COPD, etc.) had a lower PACIC score than those with cardiovascular disease. Patients with chronic respiratory were considered as vulnerable group during the pandemic, and they had difficulty in accessing healthcare services, medications, and medical devices. These patients need additional supportive care and intensive care support, and they are also at high risk of COVID-19 because of the nebulizers use. All these situations cause them to face serious COVID-19 symptoms and mortality risks when effective disease management is not provided (2,13,40,41). Therefore, it was not surprising that patients with respiratory diseases had more difficulty managing their chronic condition.

When the correlations between CORPD and PACIC total and subscale scores were examined, psychological stress and suspicion increased active participation in care; suspicion also increased problem solving and follow-up/coordination. Research results showed that moderate psychological stress and suspicion had a positive and stimulating effect on patients' chronic disease management. It is reported that until the optimum level is reached, stress can be beneficial and cause positive reactions. In addition, it is stated that the adaptation response to stress may lead to negative health outcomes but may have protective effects against another health problem on the other hand (42). It has also been reported that short-term stress has positive effects on the immune system and improving health (43). In this direction, the positive effect of moderate stress on chronic disease management was supported by the literature in this study, which evaluated the relevant population in a short period of time.

Study Limitations

This cross-sectional study was carried out using social networks from people who could be reached within a certain date range. The fact that the data were collected during the period when COVID-19 was not very widespread, the snowball sampling method used, and the majority of the participants being women, constituted limitations in terms of the generalizability of the results to the whole population. The strength of our study was that the scales of which validity and reliability studies were previously performed in Turkey were used in the study.

Conclusion

Healthcare professionals should recognize that poorly managed chronic diseases have long-term adverse effects. For this reason, it is emphasized that it is necessary to focus on patients with chronic diseases, especially in this period. It is necessary to develop a systematic framework for defining the mental effects of the pandemic in patients with chronic illness. Accordingly, in this study, psychological stress, and disease management in individuals with chronic disease were at moderate levels. Although psychological stress negatively affected people's physical well-being, social relations, and economic status in era of the pandemic, it was found that moderate stress levels positively affected chronic disease management in this study. It is recommended to develop a systematic framework for defining the mental effects of the pandemic in patients with chronic illness. It is recommended to evaluate the long-term effects of psychological stress, and its impact on chronic disease management in further research.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The scientific research ethics committee approval was obtained (no: 09/17, date: 12.04.2021).

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: K.İ., N.A.S., Concept: K.İ., N.A.S., Design: K.İ., N.A.S., Data Collection or Processing: K.İ., N.A.S., Analysis or Interpretation: K.İ., N.A.S., Literature Search: K.İ., N.A.S., Writing: K.İ., N.A.S.

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Original Article

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The Relationship Between Vitamin D Deficiency and Burnout Syndrome in Operating Room Workers: Correlational Research

Ameliyathane Çalışanlarında D Vitamini Eksikliği ile Tükenmişlik Sendromu Arasındaki İlişki: Korelasyonel Araştırma

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ABSTRACT

Objective: The aim of this study was to determine the relationship between burnout syndrome and vitamin D levels of the operating room staff who had to work indoors.

Methods: Vitamin D, phosphor, complete blood count, iron, alanine aminotransferase and aspartate amino transferase, thyroid stimulating hormone, vitamin B12 and creatinine levels were examined in the healthy staff working in the operating room (minimum 1 year) between the ages of 18-50. The General Health scale, Maslach Burnout inventory and the Beck Depression inventory (BDI) were applied to the operating room staff.

Results: There were a low degree of correlation between age and vitamin D levels, positive and modest correlation between income and emotional exhaustion, and low degree of negative correlation between personal accomplishment (PA) and sleep duration. There were low positive correlation between BDI and emotional exhaustion, low positive correlation between BDI and depersonalization, moderate positive correlation between emotional exhaustion (EE) and personal accomplishment, moderate positive correlation between EE and depersonalization, and low positive correlation between PA and depersonalization. There was no significant correlation between other variables.

ÖZ

Amaç: Bu çalışmanın amacı, kapalı alanda çalışmak zorunda olan ameliyathane personelinin tükenmişlik sendromu ile D vitamini düzeyleri arasındaki ilişkinin belirlenmesidir.

Yöntemler: Ameliyathanede çalışan (en az 1 yıl) 18-50 yaş arası sağlıklı gönüllülerin kanlarında D vitamini, hemogram, demir, alanin amino transferaz, aspartat amino transferaz, tiroid stimülan hormon, B12 vitamini ve kreatinin ölçümleri yapılmıştır. Ameliyathane personeline Genel Sağlık ölçeği, Beck Depresyon ölçeği (BDÖ) ile Maslach Tükenmişlik ölçeği uygulandı.

Bulgular: Katılımcıların D vitamini düzeyi ile yaşı arasında düşük derecede pozitif korelasyon, duygusal tükenmişlik ile gelir arasında orta derecede pozitif korelasyon, kişisel başarıda (KB) azalma ile uyku süresi arasında düşük derecede negatif korelasyon tespit edilmiştir. Ölçek puanları ve D vitamin düzeyinin aralarındaki korelasyona baktığımızda; BDÖ ile duygusal tükenmişlik arasında düşük derecede pozitif korelasyon, BDÖ ile duyarsızlaşma arasında düşük derecede pozitif korelasyon, duygusal tükenmişlik ile KB'de azalma arasında orta derecede pozitif korelasyon, duygusal tükenmişlik (DT) ile duyarsızlaşma arasında orta derecede pozitif korelasyon, KB'de azalma ile duyarsızlaşma arasında düşük derecede

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ABSTRACT

Conclusion: As a conclusion, a significant relationship could not be determined between the scores of the BDI and the emotional exhaustion, depersonalization and PA subscales of the Maslach Burnout scale and the level of vitamin D.

Keywords: Vitamin D, burnout, depression, questionnaires

ÖZ

pozitif korelasyon bulunurken diğer değişkenler arasında anlamlı bir korelasyon bulunmamıştır.

Sonuç: Sonuç olarak çalışmamızda, D vitamini düzeyi ile, Beck Depresyon ölçeği ve Maslach Tükenmişlik ölçeğinin alt boyutlarından DDT, KB'de azalma ve duyarsızlaşma puanları arasında anlamlı bir ilişki saptanamamıştır.

Anahtar Sözcükler: D vitamini, tükenmişlik, depresyon, ölçek

Introduction

Burnout Syndrome is a state of exhaustion in the internal resources of the individual as a result of failure, weariness, decrease in energy and power or unsatisfied desires, and it affects working life negatively. Vitamin D has an effect on calcium homeostasis, bone health and has a relationship with the immune system. Burnout is affecting physicians and its overall prevalence is unknown (1-3).

Operating room workers mostly work in environments that are not exposed to sunlight, under stress and anxiety.

The aim of this study was to determine the relationship between vitamin D levels, Maslach Burnout scale (MBS) and Beck depression inventory (BDI) scores in operating room workers who had to work in a sunless environment.

Methods

Study Design

Personnels who were working in the operating room for at least 1 year, between the ages of 18-50, without any bone, thyroid, pituitary, neurological, kidney or liver disease were included in the study. Vitamin D, phosphor, hemogram, iron, alanine amino transferase, aspartate amino transferase, thyroid stimulating hormone, vitamin B12 and creatinine levels were measured in the blood. The General Health Scale, BDI and MBS were used as questionnaires.

Statistical Analysis

The MedCalc statistical package program was used for statistical analyses. Paired-unique student's t-test and chi-square test were used and a p value of <0.05 was considered significant.

Results

Demographic data and findings are given in Table 1. Participants' blood values are given in Table 2. Maslach's Three-Dimensional Burnout Model considers burnout as a three-component group of psychological symptoms. Emotional exhaustion, depersonalization, and personal accomplishment (PA) (4). There are 9 items on emotional exhaustion (EE), 5 items on depersonalization (D), and 8 items on accomplishment PA on the scale. After the question items that make up the MBS are scored in the range of 0-4 points, each subscale is summed up and three separate points are obtained. By summing these scores, scores ranging from 0-36 for EE, 0-20 for D and 0-32 for PA are obtained. The EE includes feelings of being exhausted and overloaded by one's occupation; D describes the feelings of the person to be devoid of emotion and careless towards the people they serve; the PA describes the individual's feelings of overcoming problems with success (Figure 1).

When we evaluated the relationships between sociodemographic data, vitamin D level, BDI score, and EE, D and PA subscales scores of MBS; there was no statistically significant relationship between gender, marital status, having a child, profession, career choice, and leave after work shift, and vitamin D level, BDI score, and PA subscale score ($p>0.05$) (Table 3).

When EE subscale score was compared in terms of marital status and having a child, there was a statistically significant relationship ($p<0.05$), but no statistically significant relationship was found in terms of gender, profession, career choice and taking leave after work shift ($p>0.05$). When D subscale score was compared in terms of gender, marital status, profession, career choice, and taking leave after work shift, there was no statistically significant relationship ($p>0.05$), while there was a statistically significant relationship in terms of having children ($p<0.05$).

When we evaluated the participants' habits and disease status and vitamin D level, BDI score, and EE, D and PA subscales scores; no statistically significant difference was found between hobby, smoking,alcohol use, presence of chronic disease, problems experienced and coping methods, vitamin D level, PA and D subscales scores ($p>0.05$) (Table 4).

While there was a statistically significant relationship between having a problem and BDI score ($p<0.05$), there was not statistically significant relationship between hobby, smoking, alcohol use, the presence of chronic disease, and methods of coping with the problem and BDI score ($p>0.05$). While there was a statistically significant relationship between the presence of a chronic disease and EE subscale score ($p<0.05$), there was no statistically significant relationship between the hobby, smoking,alcohol use, having problems and the methods of coping with problems ($p>0.05$).

When we looked at the correlation between scale scores and vitamin D levels; low positive correlation between BDI score and EE subscale score (rho =0.281, $p<0.05$), low positive correlation

Table 1. Sociodemographic characteristics and the habits and disease status of the participants

		Number	
Gender	Male	30	
	Female	54	
Age (mean ± SD) years		30.36±6.90	
Marital status	Maried	49	
	Single	34	
	Divorced	1	
Status of having children	No	50	
	Yes	34	
Profession	Janitor	14	
	Nurse	15	
	Technician	27	
	Secretary	4	
	Resident Dr	13	
	Specialist Dr	11	
Career choice	Willingly	58	
	Influence of relative	11	
	Random	15	
Average monthly income (mean) *(TL)		4489.69	
Time in the profession (mean) *(years)		8.29	
Weekly working hours (mean) *(hours)		56.13	
Taking leave after work shift, yes/no (%)		43/28 (60.6/39.4)	
		Number	%
Do you have any hobby?	Yes	57	67.9
	No	27	32.1
Smoking status	Yes	24	28.6
	No	60	71.4
Alcohol	Yes	5	6.0
	No	79	94.0
Having a chronic disease	Yes	10	11.9
	No	74	88.1
Daily sleep time hour (mean)**		6.27	0.88
Having problems?	No	30	35.7
	Problem in work environment	35	41.7
	Health	5	6.0
	Sexuality	5	6.0
	Economy	5	6.0
	Education	4	4.8
Trouble time (mean ± SD)** hours		3	2
Methods of coping with problems	Share with someone	24	28.6
	Walk	5	6.0
	Friend	48	57.1
	Shopping	5	6.0
	Housework	2	2.4

*Mean values are given for continuous variables.
**Mean and standard deviation (SD) are given for continuous variables.

Table 2. Participants' blood values

	Mean	Standard deviation	Minimum	Maximum
Vitamin D ng/mL	8.53	5.15	2.50	29.00
Glucose mg/dL	90.90	13.52	70.00	141.00
Urea mg/dL	25.61	7.44	11.00	49.00
BUN mg/dL	11.67	3.43	5.00	22.00
Creatinine mg/dL	0.69	0.12	0.50	1.00
EGFR mL/min/1.73 m^2	116.24	9.98	86.00	141.00
AST U/L	17.64	5.97	8.00	36.00
ALT U/L	18.39	10.13	6.00	53.00
Ca mg/dL	9.67	0.37	8.70	10.60
Phosphor mg/dL	3.67	0.56	2.50	5.50
Iron ug/dL	78.02	36.53	15.00	185.00
Iron binding capacity ug/dL	379.22	51.89	251.00	606.00
UIBC ug/dL	303.40	72.51	146.00	541.00
Leukocyte 10*3/uL	7.11	1.80	3.20	12.40
Hemoglobin g/dL	13.54	1.60	10.20	17.00
Hematocrit %	41.03	4.41	32.00	50.00
PLT 10*3/uL	245.29	50.40	146.00	403.00
TSH uIU/mL	1.54	0.87	0.30	4.90
PTH pg/mL	65.42	59.61	17.00	541.00
Ferritin ng/mL	40.68	42.88	5.90	234.00
Vitamin B12 pg/mL	314.52	97.13	130.00	642.00

BUN: Blood urea nitrogen, EGFR: Estimated glomerular filtration rate, AST: Aspartate transaminase, ALT: Alanine transaminase, PLT: Platelet, TSH: Thyroid-stimulating hormone, PTH: Parathyroid hormone

Table 3. Evaluation between the sociodemographic data of the participants and their vitamin D level, Beck depression inventory, and the sub-dimensions of Maslach Burnout scale: emotional exhaustion, personal accomplisment, and depersonalization scores

		Vitamin D		BDI		Emotional exhaustion		Personal accomplisment		Depersonalization	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Gender	Male	9.15	4.72	13.59	7.07	13.47	5.79	11.03	4.84	5.30	2.96
	Female	8.19	5.39	11.09	6.35	15.07	6.29	12.04	4.12	5.11	2.91
	P	0.156*		0.105†		0.252†		0.344*		0.642*	
Marital status	Maried	9.35	6.09	12.29	6.69	13.14	5.87	11.16	4.33	4.80	2.79
	Single, widow	7.39	3.19	11.51	6.72	16.40	6.05	12.40	4.43	5.71	3.03
	P	0.268*		0.603†		**0.015†**		0.327*		0.279*	
Status of having children	No	7.90	4.46	11.48	6.68	15.82	6.21	12.24	3.91	6.00	3.03
	Yes	9.45	5.98	12.70	6.69	12.56	5.53	10.85	4.95	3.97	2.28
	P	0.407*		0.419†		**0.016†**		0.208*		**0.005***	
Profession	Auxiliary staff	9.82	6.81	10.53	6.54	12.11	4.64	12.72	5.39	4.39	2.57
	Health personnel	8.18	4.60	12.33	6.71	15.15	6.35	11.39	4.07	5.39	2.98
	P	0.407*		0.323†		0.062†		0.145*		0.348*	
Career choice	Willing	8.48	5.49	11.79	6.32	14.47	6.34	11.09	4.30	5.14	2.79
	Influence of relative	9.25	5.69	11.73	8.88	15.64	7.17	11.91	4.74	5.27	4.03
	Random	8.19	3.30	12.80	6.60	13.80	4.52	13.80	4.04	5.27	2.63
	P	0.516**		0.869††		0.754††		0.091**		0.913**	
Taking leave after work shift	Yes	7.88	3.50	11.71	6.43	14.42	5.86	11.65	4.05	5.42	2.92
	No	8.92	5.72	14.04	6.22	15.54	6.17	12.29	4.61	5.46	2.71
	P	0.746*		0.139†		0.445†		0.489*		0.910*	

*Mann-Whitney U, **Kruskal-Wallis test, †T-test in independent groups, ††ANOVA, BDI: Beck depression inventory

Table 4. Evaluation between the participants' habits and disease status and their vitamin D level, Beck depression inventory, and emotional exhaustion, personal accomplisment and depersonalization scores, which are the sub-dimensions of the Maslach Burnout scale

		Vitamin D		BDI		Emotional exhaustion		Personal accomplisment		Depersonalization	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Do you have any hobby?	Yes	8.08	3.87	11.91	7.14	14.42	6.68	11.19	4.84	5.26	3.23
	No	9.48	7.14	12.08	5.63	14.67	4.87	12.70	3.06	5.00	2.15
	p	0.719*		0.918†		0.865†		0.197*		0.877*	
Smoking status	Yes	8.96	4.26	13.83	7.41	15.00	6.30	12.12	5.57	6.17	3.33
	No	8.36	5.49	11.20	6.26	14.30	6.10	11.50	3.85	4.78	2.66
	p	0.203*		0.104†		0.639†		0.235*		0.063*	
Alcohol	Yes	10.16	4.80	15.20	8.14	16.40	5.37	12.40	5.98	6.20	3.90
	No	8.46	5.21	11.73	6.61	14.32	6.20	11.56	4.30	5.08	2.86
	p	0.221*		0.265†		0.466†		0.392*		0.520*	
Having a chronic disease	Yes	9.45	7.43	15.10	7.98	18.10	6.59	13.40	5.54	4.90	3.48
	No	8.41	4.82	11.53	6.42	14.01	5.94	11.45	4.20	5.22	2.85
	p	0.804*		0.114†		**0.047†**		0.170*		0.500*	
Having problems?	No	8.24	4.83	9.03	6.16	12.80	6.30	10.30	4.59	4.63	2.83
	Working environment	8.49	4.95	12.91	6.62	15.29	5.99	11.83	3.54	5.40	3.00
	Healthy, sexuality	10.00	8.28	15.10	6.61	17.50	6.17	14.10	6.15	6.40	3.50
	Economy, education	8.03	2.51	14.22	5.95	13.78	4.97	13.00	3.28	4.78	1.86
	p	0.952**		**0.020††**		0.143††		0.152**		0.398**	
Methods of coping with problems	With someone, friend	8.89	5.43	11.88	6.56	14.04	5.99	11.68	4.43	4.90	2.83
	Walk	5.98	2.98	18.25	9.32	20.40	6.88	10.80	4.76	8.40	2.51
	Shopping	6.42	1.43	9.20	5.63	14.60	6.11	11.80	5.07	5.60	3.51
	Housework	7.20	0.28	9.50	0.71	16.00	5.66	13.50	0.71	6.00	0.00
	p	0.495**		0.196††		0.160††		0.935**		0.062**	

*Mann-Whitney U, **Kruskal-Wallis test, †t-test in independent groups, ††ANOVA, BDI: Beck depression inventory, SD: Standard deviation

between BDI score and D subscale score (rho =0.238, p<0.05), moderate positive correlation between EE and PA subscales scores (rho =0.342, p<0.05), moderate positive correlation between EE and D subscales scores (rho =0.582, p<0.05), and low positive correlation between PA and D subscales scores (rho =0.285, p<0.05) were found. No significant correlation was found between other variables.

When we took the cut-off scoreof the BDI as 17 and compared it with MBS's subscales scores and vitamin D level; there were statistically significant relationships between EE subscale score and BDI subscale score, and between PA and D subscales scores (p<0.05). No statistically significant relationship was found between other scale scores and vitamin D level (p>0.05) (Tables 5, 6).

Discussion

Burnout syndrome (BS) is a condition that can be seen in jobs where working hours are long and accompanied by stress, negatively affecting both the work and private life of hospital staff. The presence of vitamin D receptors in depression-related regions such as the prefrontal cortex, hippocampus, cingulate gyrus, thalamus, and hypothalamus suggests that vitamin D may be involved in the etiology of depression (5).

In a comprehensive study including 7,970 participants in the USA, it was stated that vitamin D deficiency increased the susceptibility to depression (6). A similar study in the Netherlands in which 1,282 older adults (65-95 years old) participated supported those results (7). Studies investigating the relationship between depression and burnout suggested that there was a relationship between depression and burnout (8). Considering these results, it can be mentioned that there is a relationship between BS and vitamin D deficiency. However, there are no studies directly investigating vitamin D deficiency and BS.

Considering the studies examining the burnout status of those working in the field of anesthesia, it was observed that the participants consisted of anesthesiologists or assistants. In some studies, the participants consisted only of nurses or anesthetic

Table 5. Comparison of scale scores and vitamin D levels with sociodemographic data

		Age	BMI	Year	Working hour	Sleep	Income
Vitamin D	rho	0.249*	0.133	0.174	-0.07	-0.026	0.031
	p	**0.023**	0.226	0.113	0.528	0.814	0.781
BDI	rho	0.038	0.095	-0.04	0.169	-0.157	0.169
	p	0.735	0.395	0.718	0.126	0.157	0.127
Emotional exhaustion	rho	-0.054	0.152	-0.122	0.099	-0.108	0.309**
	p	0.625	0.167	0.269	0.369	0.328	**0.004**
Personal accomplisment	rho	0.089	0.096	-0.068	0.144	-0.216*	-0.102
	p	0.421	0.386	0.539	0.191	**0.048**	0.358
Depersonalization	rho	-0.079	0.102	-0.136	-0.004	-0.16	0.159
	p	0.477	0.354	0.216	0.97	0.145	0.147

BMI: Body mass index, BDI: Beck depression inventory

Table 6. Correlation comparison between scale scores and vitamin D levels

		Vitamin D	BDI	Emotional exhaustion	Personal accomplisment	Depersonalization
Vitamin D	rho		-0.061	-0.109	0.102	-0.081
	p		0.583	0.323	0.358	0.466
BDI	rho	-0.061		0.281	0.101	0.238
	p	0.583		**0.01**	0.364	0.03
Emotional exhaustion	rho	-0.109	0.281		0.342	0.582
	p	0.323	**0.01**		**0.001**	**0.001**
Personal accomplisment	Rho	0.102	0.101	0.342		0.285
	p	0.358	0.364	**0.001**		**0.009**
Depersonalization	rho	-0.081	0.238	0.582	0.285	
	p	0.466	**0.03**	**0.001**	**0.009**	

BDI: Beck depression inventory

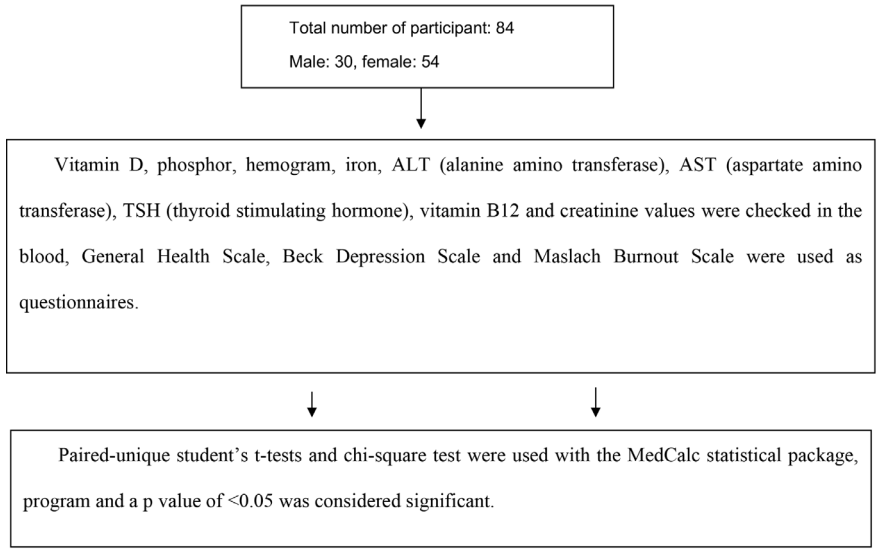

Figure 1. Flow chart for this correlational research

technicians working in the field of anesthesia, while in some studies both anesthesiologists and anesthesia nurses were included. In our study, unlike the other studies in the literature, personnel, technicians, and secretaries working in the operating room were also included, apart from the anesthesiologists and nurses (9-12). With this feature of our study, we think that it is an inclusive study for all employees working in the operating room. Studies suggest that anesthesiologists have a high risk for burnout (13).

In a study conducted with physicians who received assistant training in the field of anesthesia, it was stated that female physicians had a higher risk of BS and depression compared to males (14). In another study investigating BS of anesthesiologists, it was stated that gender was not important for BS (15). In our study, there was no relationship between vitamin D level, BDI score, MBS's subscales scores and gender of the physicians.

It has been reported in studies that the marital status of anesthesiologists are not correlated with MBS's subscales scores (10,15,16). In our study, similar results were found with the studies in the literature, except for EE subscale score. In our study, EE subscale score was found to be higher in single and divorced anesthesia workers. Some authors have emphasized that the level of burnout is related to the number of children rather than having children. In the same study, it was stated that anesthesiologists had lower burnout scores if they had two or more children compared to individuals without children (10). In a study evaluating the burnout status of 1,508 anesthesiologists, it was stated that anesthetists who were parents showed lower depression and BS characteristics (14). In our study, however, no difference was found between having a child and the status of vitamin D, BDI score, and PA subscale score. In addition, our study shows similar results with the studies in the literature in terms of D and EE subscales scores.

As age increases, the concentration of 7-dehydrocholesterol, a precursor of vitamin D, decreases in the skin. This reduces the skin's capacity to synthesize vitamin D. In our study, contrary to this literature finding, a slight positive correlation was found between the ages of the participants and their vitamin D levels. One of the two main sources of vitamin D is exposure to sunlight, while the other is food (17,18). It is thought that those who have to work for a long time in closed areas away from sunlight will have deficient vitamin D levels in their bodies. Operating room workers stay in closed environments for a long time. In order to determine vitamin D excess or deficiency, 25-hydroxyvitamin D levels are checked.

25-hydroxyvitamin D level;

• Vitamin D deficiency, if it is less than 20 ng/mL,

• Vitamin D insufficiency between 21 and 29 ng/mL,

• Normal vitamin D level, if it is higher than 30 ng/mL,

• Vitamin D intoxication, if it is higher than 150 ng/mL (19). In our study, the mean vitamin D level was 8.53±5.15.

There are no systematic studies investigating vitamin D level and BS in the literature. The results of our research can contribute to the literature. In our study, no relationship was found between vitamin D levels and PA and D subscales scores. A relationship was found between vitamin D level and EE subscale score.

The MBS, which evaluates EE, D and PA, is an important scale that evaluates the general burnout status of the person. As in our study, it is expected that the subscales evaluating different dimensions of burnout are in a positive correlation with each other.

Some studies show that vitamin D deficiency is a facilitating factor for depression (20). In our study, when the cut-off point was taken as 17, no correlation was found between vitamin D level and having depression. There was no correlation between vitamin D level and MBS's subscales scores.

It has been reported in studies that the marital status of anesthesiologists is not correlated with MBS's subscales scores. In our study, similar results were found with the studies in the literature, except for EE subscale score. In our study, EE subscale score was found to be higher in single and divorced anesthesia workers. In our study, divorced and single participants were considered together. Considering this information in the literature, not examining divorced and single people separately could be considered as a limitation of our study. Our study created a different information from the literature in the general population of those working in the operating room environment.

Conclusion

In conclusion, in our study, there was no significant relationship between vitamin D level and BDI score and PA and D subscales scores, while a relationship was found between vitamin D level and EE subscale score.

Ethics

Ethics Committee Approval: The study was conducted after the approval of the Bezmialem Vakıf University Clinical Research Ethics Committee, with desicion number 24/17 and dated 30.12.2015.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: G.B., M.Ç., M.Çal., K.K., Design: G.B., F.D., K.K., Data Collection or Processing: Z.S.A., Analysis or Interpretation: Z.S.A., G.B., M.Çal., Literature Search: Z.S.A., M.Çal., Writing: G.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

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Are Refugee and Native Patients' Self-Care Agencies the Same?-A Cross-sectional Study in Chronic Hemodialysis Patients in Turkey

Mülteci ve Yerli Hastaların Özbakım Güçleri Aynı Mı?-Türkiye'deki Kronik Hemodiyaliz Hastalarında Kesitsel Bir Çalışma

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ABSTRACT

Objective: It was aimed to compare self-care agency of refugee and native populations in chronic hemodialysis patients.

Methods: The study was conducted with 33 refugees and 48 native patients in the hemodialysis unit of a training and research hospital in our country. Data were collected through face-to-face questionnaire. IBM SPSS statistics program was used to evaluate the data.

Results: In the study, there was a significant difference between two populations in terms of drug use (p=0.041, p<0.05) and self-monitoring (p=0.048, p<0.05), which were sub-dimensions of the self-care scale, but there was no significant difference between two populations in terms of the total self-care agency scores (p=0.768). It was determined that there was no significant correlation between the sub-dimensions of self-care agency and the year the refugees lived in our country and the months they underwent hemodialysis (p>0.05).

Conclusion: It was observed that in chronic hemodialysis patients, the situation of meeting their self-care was the same in the refugee and native populations, while the refugees were insufficient in the use of drugs and the native population in self-monitoring. It is thought that it is necessary to get support from a hospital interpreter in order to eliminate language problems while giving self-care training to refugees, and it is thought that it will be appropriate to conduct the study with groups with different chronic diseases.

Keywords: Hemodialysis, population groups, self care

ÖZ

Amaç: Kronik hemodiyaliz hastalarında mülteci ve yerli popülasyonun özbakım güçlerinin karşılaştırılması amaçlanmıştır.

Yöntemler: Çalışma ülkemizde bir eğitim ve araştırma hastanesinin hemodiyaliz ünitesinde 33 mülteci, 48 yerli hasta ile yapılmıştır. Veriler yüz yüze anket yolu ile toplanmıştır. Verilerin değerlendirilmesinde IBM SPSS statistics programı kullanılmıştır.

Bulgular: İki grup arasında, özbakım gücü ölçeği alt boyutlarından ilaç kullanımı (p=0,041, p<0,05) ve kendini izleme (p=0,048, p<0,05) açısından anlamlı fark olduğu, özbakım gücü toplam puanlar arasında anlamlı fark olmadığı (p=0,768), özbakım gücü alt boyutları ile mültecilerin ülkemizde yaşadığı yıl ve hemodiyalize girdikleri aylar arasında anlamlı ilişki olmadığı (p>0,05) tespit edilmiştir.

Sonuç: Kronik hemodiyaliz hastalarında mülteci ve yerli popülasyonda özbakımlarını karşılama durumlarının aynı olduğu, mültecilerin ilaç kullanımı, yerli popülasyonun ise kendi kendini izleme durumlarında yetersiz oldukları görülmüştür. Mültecilere özbakımları ile ilgili eğitimlerini verirken dil problemlerinin ortadan kalkması için hastane tercümanından destek alınması gerektiği ve çalışmanın farklı kronik hastalığı olan gruplarla da yapılmasının uygun olacağı düşünülmektedir.

Anahtar Sözcükler: Hemodiyaliz, nüfus grupları, özbakım

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Introduction

Chronic kidney disease (CKD) is a serious health problem that is common all over the world and its prevalence is increasing as the years progress. According to the report published by the U.S. Department of Health and Human Services, the prevalence of CKD was 13.3% between 2005-2008, 12.5% between 2009-2012, 13.9% between 2013-2016 and 14% between 2017-2020 (1). It is seen that hemodialysis is frequently used in the replacement treatment of chronic renal failure (2). According to 2016 data, there were 75,000 patients who underwent dialysis or kidney transplantation in our country (3). Cervantes et al. (4) found that the average 5-year relative risk of death for undocumented immigrants undergoing emergency hemodialysis was more than 14 times higher than those receiving standard hemodialysis.

There has been a great increase in the number of refugees coming to our country due to the increasing war, conflict and political reasons in the world, especially since 2011 (5). Syrians constitute the largest share in the number of refugees in Turkey. The official number of Syrians announced in November 2022 in our country is 3,577,714 people (6). Syrians are in temporary protection status in our country and their health expenses are covered by our country (7). However, studies have shown that although health expenditures are covered by our country, Syrians have some difficulties in accessing health services (8,9). The aim of hemodialysis treatment should be to provide self-care as well as medical treatment of patients (10). Self-care is activities initiated and performed by individuals themselves to maintain life, health and well-being. Self-care agency is the individual's ability to initiate or implement health activities to maintain his or her life, health and well-being (11).

When we look at the literature, there are many studies that study refugees undergoing hemodialysis (12-14). However, there has not been any study evaluating the self-care abilities of the refugee and native populations receiving chronic hemodialysis, and it is thought to contribute to the literature.

Methods

Study Design

The study was descriptive and cross-sectional.

Sample of the Research

The sample of the study consisted of 33 refugee and 48 native hemodialysis patients aged 18 and over who accepted to undergo hemodialysis in the dialysis unit of a training and research hospital in Turkey. Participants aged 18 and over who voluntarily agreed to participate in the study were informed about the research and their rights, and their "informed consent" was obtained before the research. All the rights of the participants were respected and the principles of voluntariness and confidentiality were paid attention to.

Data Collection Method

Data were collected by face-to-face survey method between 02 March-15 March 2023. While collecting the questionnaires of the refugees, support was obtained from the translator of the hospital.

Data Collection

While collecting the data, a form describing the personal characteristics of the patients and the Self-Care Agency Scale (SCAS) for Chronic Hemodialysis Patients were used.

Personal Data Identification Form of Patients

The data was created by scanning the literature and consisted of 7 items related to age, gender, educational status, marital status, definition of refugee and native population, years on hemodialysis and years the refugees lived in Turkey.

Self-care Agency Scale for Chronic Hemodialysis Patients

The SCAS was developed by Ören and Enç (15) in 2010 and its validity and reliability study in Turkish was performed. In Ören and Enç (15) study, it was stated that Cronbach's alpha values were between 0.56 and 0.68 on the basis of sub-dimensions and 0.75 in the whole scale. SCAS consists of 22 items. It is a three-point Likert scale scored between 0 and 2. The statements in the scale consist of 5 sub-dimensions related to the use of drugs, diet, self-monitoring of the patient, hygienic care and mental state. Low scores obtained from the scale are considered as poor self-care agency, and high scores are considered good (15). In this study, the Cronbach's alpha coefficient of SCAS was determined as 0.72.

Statistical Analysis

IBM SPSS statistics 22.0 program was used for statistical analysis in the study. While evaluating the study data, in addition to descriptive statistical methods (mean, standard deviation, frequency, percent), the Student t-test was used to compare normally distributed data, and the Mann-Whitney U test was used to compare data that did not show normal distribution. Pearson and Spearman correlation analyses were used to evaluate the correlation between variables. The results were evaluated at the 95% confidence interval and the significance level of $p<0.05$.

Ethical aspect of the study: Before starting the study, permission was obtained from the Clinical Research Ethics Committee of University of Health Sciences Turkey, İstanbul Haseki Training and Research Hospital with the date of 01.03.2023 and the decision number 06-2023. Permission was also obtained from the scale's authors. Participants who voluntarily accepted to participate in the study were informed about the research and their rights as necessary, and their "informed consent" was obtained before the research. All the rights of the participants were respected and the principles of voluntariness and confidentiality were paid attention to.

Results

The descriptive characteristics of the refugee and native populations in chronic hemodialysis patients are shown in Table 1. It was determined that 51.5% of the refugee population of the participants were women, 87.9% were married, 27.2% had

primary school education, average age was 49.06±15.68, the number of years that refugees lived in Turkey was 6.65±2.51 years in Turkey, and they had undergone hemodialysis for 33.93±21.93 months. On the other hand, 60.4% of the native population were male, 77.1% were married, 45.8% had primary school education, mean age was 54.54±16.76 and they had undergone hemodialysis for 23.84±23.08 months (Table 1).

Table 2 shows whether there is a significant difference between the two populations in the mean scores and mean scores of SCAS and its sub-dimensions applied to the refugee and native populations in chronic hemodialysis patients. Although there was no significant difference between the two populations in terms of the total scores of self-care agency (p=0.768, p<0.05), a significant difference was found between the groups in terms of drug use (p=0.041, p<0.05) and self-monitoring (p=0.048, p<0.05), which were sub-dimensions of SCAS (Table 2).

In chronic hemodialysis patients, the correlation between the sub-dimensions of self-care ageny in the refugee and native populations and the years the refugees lived in Turkey and the months both groups had been on hemodialysis was examined (Table 3). There was no significant correlation between the sub-dimensions of the scale and the months of undergoing dialysis and the years they lived in Turkey (p<0.05) (Table 3).

Discussion

Correlation findings between the descriptive characteristics of the refugee and native populations in chronic hemodialysis patients (Table 1), the total scores and sub-dimensions scores obtained from SCAS its (Table 2), the years they lived in Turkey and the months they were on dialysis (Table 2) were given (Table 3). When we look at the literature, no study has been found that compares the self-care agency of refugee and native populations in chronic hemodialysis patients. The findings of the study will be compared with the self-care agency scores of the patients identified in the literature. In the study conducted by Aydın and Sayılan (16) on 125 patients aged 65 and over, the mean self care

Table 1. Descriptive characteristics of refugee and native populations in chronic hemodialysis patients (n=81)

n	Refugees (n=33)		Natives (n=48)	
	%	n	%	
Gender				
Female	17	51.5	19	39.6
Male	16	48.5	29	60.4
Age (average)	49.06±15.68		54.54±16.76	
Marital status				
Married	29	87.9	37	77.1
Single	4	12.1	11	22.9
Educational status				
Illiterate	8	24.2	11	22.9
Literate	5	15.2	0	0
Primary	9	27.3	22	45.8
Middle school	7	21.2	2	4.2
High school	3	9.1	9	18.8
Bachelor degree	1	3	4	8.3
The years they lived in Turkey	6.65±2.51		-	
The months they were on dialysis	33.93±21.93		23.84±23.08	

Descriptive statistical methods (mean, standard deviation, frequency, percent)

Table 2. Self-care agency scale sub-dimensions and total score averages of refugee and native populations in chronic hemodialysis patients (n=81)

Scale sub-dimensions	Min-max points	Refugees (n=33)	Natives (n=48)	p*
Drug use	0-12	7.45±1.78	7.58±2.58	0.041
Diet	0-10	6.39±1.58	6.42±1.83	0.732
Self monitoring	0-8	5.97±1.31	5.1±1.98	0.048
Hygienic care	0-8	6.18±1.48	6.42±1.56	0.396
Mental state	0-6	2.91±1.56	2.96±1.78	0.454
Total	0-44	28.91±4.68	28.52±6.44	0.768

The Student t-test and The Mann-Whitney U test
Min: Minimum, Max: Maximum

Table 3. Correlation between scale sub-dimensions of self-care agency in refugee and native populations in chronic hemodialysis patients, the years they lived in Turkey and the months they were on dialysis

		Refugees		Natives	
Scale sub-dimensions and total		The years they lived in Turkey	The months they were on dialysis	The years they lived in Turkey	The months they were on dialysis
Drug use	r	0.116	0.204	-	0.169
	p	0.519	0.255	-	0.182
Diet	r	-0.248	0.156	-	-0.024
	p	0.165	0.387	-	0.869
Self monitoring	r	0.129	0.153	-	0.230
	p	0.473	0.395	-	0.116
Hygienic care	r	-0.074	0.178	-	0.271
	p	0.681	0.321	-	0.062
Mental state	r	0.099	0.186	-	0.114
	p	0.585	0.300	-	0.440
Total	r	0.007	0.292	-	0.240
	p	0.971	0.099	-	0.100

Pearson and Spearman correlation analyses

agency score was 90.00±19.95 [maximum (max) score: 140], and in the randomized controlled study conducted by Deveci and Aydın (17) on 70 hemodialysis patients, it was determined that the mean self care agency score of the intervention group (n=35) was 86.20±16.00, and the mean self care agency score of the control group (n=35) was 79.11±14.65 (max: 136 points). In the study conducted by Du et al. (18) on 472 elderly patients in China, it was 106.12±19.47 (max: 172 points), while in the study conducted by Demir Gökmen and Fırat (19) on 146 patients with COPD, it was 73.09±14.153 (max: 140 points) (and in the study conducted by Türker et al. (20) on 126 hemodialysis patients, it was found to be 51.01±27.33 (max: 134 points). In this study, SCAS score of the refugee population was determined as 28.91±4.68, and SCAS score of the native population was 28.52±6.44 (max: 44 points). When the studies in the literature and the self-care measurement tools used in those study were examined, it was seen that different self-care agency scales were used, and their maximum mean scores were different. When the mean scores of self-care agency were evaluated with the scale of each study, it was determined that the mean score of self-care agency was moderate. In this direction, when the results of the studies in the literature were compared with this study, it was seen that the results of the literature supported the results found in this study.

In the study, no significant relationship was found between the refugee and native populations in terms of both the mean scores of self-care agency (p=0.768) (Table 2), the scale sub-dimensions of both groups, the months of undergoing dialysis and the years they lived in Turkey (Table 3). Although it has been determined in the literature studies that refugees have difficulties in accessing health services, the findings of the study show that refugees receive services in the same way as the native population (8,9). The reason for the difference from the literature might be that hemodialysis patients constituted the sample group in the study, and when it was considered that the patients would die when hemodialysis treatment was not performed, it could be considered that patients' reach to treatment was mandatory.

In the study, it was determined that there was a significant difference between the refugee and native populations in terms of the sub-dimensions of SCAS, use of drugs (p=0.041, p<0.05) and self-monitoring (p=0.048, p<0.05) (Table 2). Drug use was found to be higher in the native population than in the refugees. In studies conducted in our country, it has been stated that refugees have language problems (21-23). Drug use, which is the sub-dimension of self-care agency, is proportional to the success of the education given to the patient (24). When the patient cannot receive adequate education due to language problems, they may be insufficient in their drug use. Refugees' self-monitoring was found to be higher than the native population. Considering the ages of the refugees and the native population (Table 1), it was seen that the average age of the refugees was 49.06±15.68, while the average age of the native population was 54.54±16.76, and it was seen that the refugees were younger. The fact that the self-monitoring of refugees is higher than the native population can be attributed to the fact that they are younger. The limitations of our study were the small number of patients and the fact that the study was conducted in a single center.

Conclusion

As a result, the status of meeting self-care in the refugee and native populations is the same in chronic hemodialysis patients, while the refugees are inadequate in drug use and the native population in self-monitoring. We think that support from a hospital translator should be sought in order to reduce language problems while providing self-care training to refugees, and that more clear results can be achieved in future through multicenter studies with larger samples.

Ethics

Ethics Committee Approval: Before starting the study, permission was obtained from the Clinical Research Ethics Committee of University of Health Sciences Turkey, İstanbul Haseki Training and Research Hospital with the date of 01.03.2023 and the decision number 06-2023.

Informed Consent: Permission was also obtained from the scale's authors.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: N.K., E.C., A.Ş., Concept: N.K., E.C., Design: N.K., E.C., İ.Ç., Data Collection or Processing: N.K., İ.Ç., A.Ş., Analysis or Interpretation: N.K., Literature Search: N.K., M.R., Writing: N.K., M.R.

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Original Article

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Heat Stress Alters Oxidative and Inflammatory Responses in Many Tissues of Male Rats

Sıcaklık Stresi, Erkek Sıçanların Birçok Dokusunda Oksidatif ve Enflamatuvar Yanıtları Değiştirir

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ABSTRACT

Objective: High ambient temperature beyond the comfort zone causes environmental heat stress (HS). A large number of free radicals are produced as a response to stress. This situation can cause morbidity and mortality in humans and animals. The current study was conducted to determine the effects of HS on antioxidant status, immune response and related factors.

Methods: In the study, 18 Sprague Dawley male rats were used as animal materials. Rats were randomly assigned to Thermo-neutral group (TN; untreated at normal ambient temperature of 24±2 °C), Heat-stress 1 group (HS1; 8 hours daily exposure at 30 °C) and Heat-stress 2 group (HS2; 8 hours daily exposure at 35 °C). At the end of HS application (day 14), rats were sacrificed under ether anesthesia and brain, duodenum, heart, liver, thyroid and testis tissues were taken. The biochemical and inflammatory responses of the tissues were analyzed with the ELISA Kit.

Results: Compared to the control group; Myeloperoxidase activity was higher in the heart tissue of HS2 group ($p<0.05$). Superoxide dismutaz activity was higher in the brain and testis tissues in HS2 group ($p<0.05$). Interleukin (IL)-2 level was higher in the duodenum and testis tissue of HS1 group and lower in the liver tissue ($p<0.05$). IL-6 level was higher in the brain and heart tissue of HS2 group ($p<0.05$). Tumor necrosis factor-α concentration was lower in the brain tissue in HS1 group, higher in the duodenum tissue in HS2 group and testicular tissue in HS1 group ($p<0.05$).

Conclusion: These results showed that HS adversely affected the oxidant/antioxidant status of brain, heart and testis tissues of rats and immune response of brain, duodenum, heart, liver and testis

ÖZ

Amaç: Konfor bölgesinin ötesindeki yüksek ortam sıcaklığı, çevresel sıcaklık stresine (HS) neden olur. Strese tepki olarak çok sayıda serbest radikal üretilir. Bu durum insanlarda ve hayvanlarda morbidite ve mortaliteye neden olabilir. Mevcut çalışma, HS'nin antioksidan durumu, bağışıklık tepkisi ve ilgili faktörler üzerindeki etkilerini belirlemek için yapılmıştır.

Yöntemler: Çalışmada hayvan materyali olarak 18 adet Sprague Dawley erkek sıçan kullanıldı. Sıçanlar rastgele olarak Termo-nötr grup (TN; HS uygulanmamış ve 24±2 °C normal ortam sıcaklığında işlem görmemiş), HS1 (HS1; 30 °C'de 14 gün boyunca günde 8 saat maruziyet) ve HS2 grubu (HS2; 35 °C'de 14 gün boyunca günde 8 saat maruziyet) olmak üzere 3 gruba ayrıldı. HS uygulaması sonunda (14. gün) eter anestezisi altında sıçanlar sakrifiye edildi ve beyin, duodenum, kalp, karaciğer, tiroid ve testis dokuları alındı. Dokuların biyokimyasal ve enflamatuvar yanıtları ELISA Kit ile analiz edildi.

Bulgular: Kontrol grubu ile karşılaştırıldığında; HS2 grubunun kalp dokusunda miyeloperoksidaz aktivitesi yüksekti ($p<0,05$). HS2 grubunda beyin ve testis dokularında süperoksit dismutaz aktivitesi yüksekti ($p<0,05$). İnterlökin (IL)-2 düzeyi HS1 grubunun duodenum ve testis dokusunda yüksek, karaciğer dokusunda düşüktü ($p<0,05$). HS2 grubunun beyin ve kalp dokusunda IL-6 düzeyi yüksekti ($p<0,05$). Tümör nektroz faktör-α konsantrasyonu HS1 grubunda beyin dokusunda düşük, HS2 grubunda duodenum dokusunda yüksek ve HS1 grubunda testis dokusunda yüksek bulundu ($p<0,05$).

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ABSTRACT

tissues; also showed that the negative effects of exposure to HS were related to the severity of the stress in the heart, liver and testicular tissues.

Keywords: Immune function, climate change, oxidative stress, heat stress

ÖZ

Sonuç: Bu sonuçlar, HS'nin sıçanların beyin, kalp ve testis dokularının oksidan/antioksidan durumunu ve beyin, duodenum, kalp, karaciğer ve testis dokularının bağışıklık tepkisini olumsuz etkilediğini; ayrıca HS'ye maruz kalmanın olumsuz etkilerinin kalp, karaciğer ve testis dokularında stresin şiddeti ile de ilişkili olduğunu göstermiştir.

Anahtar Sözcükler: Bağışıklık fonksiyonu, iklim değişikliği, oksidatif stres, sıcaklık stresi

Introduction

Stress is defined as any internal or external stimulus that produces a biological response. The impact of stress varies based on the type, timing, and severity of the stimulus applied. It can result in anything from alterations in homeostasis to life-threatening consequences, and in extreme cases, death (1). The stress response is a multifaceted complex mechanism that depends on many factors such as environmental variables (ambient temperature, humidity, solar radiation and air movement) and living factors (species, breed, age, health and physiological status) (2-4).

The range of environmental temperatures in which organisms comfortably perform their regular physiological activities is termed the "thermal neutral zone" or "comfort zone". One of the primary determinants of this zone is air temperature. Disruptions occur when the ambient temperature surpasses 25°C, disrupting the equilibrium between body temperature and body heat release. This condition, known as heat stress (HS), poses risks to human and animal health, leading to substantial economic losses in public health services and livestock production (5-7).

Numerous studies report that HS causes endocrine system disorders, electrolyte imbalance, immune system disorders, and lipid and protein oxidation (8-10). Additionally, HS is associated with oxidative stress (OS), marked by an upsurge in the production of reactive oxygen species (ROS) and a decline in antioxidant capacity (11,12). OS arises as a result of an imbalance between ROS production and the antioxidant defense against them. OS, which can cause damage to biomacromolecules such as DNA, proteins and lipids, can also result in cell dysfunction and tissue damage. OS induced by free radicals can cause many diseases such as cancer, Alzheimer's disease and autoimmune diseases as well as leading to degenerative processes (12-14).

Tissue myeloperoxidase (MPO), a marker of neutrophil migration, plays an important role in oxidant production by neutrophils. MPO enzyme is a lysosomal enzyme secreted from leukocytes in response to active stress. In the event of inflammation, MPO is released into the extracellular environment. Therefore, measurement of MPO activity as an indicator of neutrophil secretion is a sensitive test (15). Superoxide dismutase (SOD) is an enzyme that catalyzes the dismutation of oxygen and hydrogen peroxide and is a primary protector against oxyradicals. SOD is an important antioxidant for superoxide, one of the main ROS in the cell (16). HS can stimulate systemic release of endogenous molecules and trigger local and systemic release of both pro- and anti-inflammatory cytokines such as interleukin (IL)-1 beta, IL-2, IL-6 and tumor necrosis factor (TNF)-α (17).

HS acts as the major challenge for maintaining the immune status in living organism. Acute HS may have a stimulatory effect on the immune system, however chronic HS may have an inhibitory role on the capacity of the immune system to maintain homeostasis (18). In addition, the negative impact of HS is predicted to worsen with the global warming (19).

This study aims to elucidate the effects of elevated temperature stress, specifically at 30°C and 35°C, on OS and inflammation biomarkers across different tissues. The selected parameters for this study are geared towards assessing inflammation and OS. TNF-α, IL-2, and IL-6 were chosen to probe inflammatory pathways, with MPO activity reflecting pro-oxidant processes, and SOD representing the enzymatic component of antioxidant activities.

Methods

In this study, 18 male Sprague Dawley rats from Atatürk University Experimental Animal Research Center were used. The Atatürk University local ethic committee for animal experiments approved the study, with protocol number: 2019-16/238.

Animals and Experimental Design

Eighteen Sprague Dawley male rats weighing between 250-300 g were randomly divided into three groups with six rats in each group. The groups were determined as Thermo-neutral (TN), 30 °C HS1 and 35 °C HS2.

Thermo-neutral (TN) group: The rats in this group were housed at room temperature at 22-24 °C for 24 hours/day and were fed with a normal diet and standard conditions were applied.

Temperature stress (HS1) group: The rats in this group were exposed to a temperature of 30 °C for 8 hours (20) a day (9:00 to 17:00/whole study) in wire cages in temperature-controlled rooms for fourteen days.

Temperature stress (HS2) group: The rats in this group were exposed to a temperature of 35 °C for 8 hours a day (from 9:00 to 17:00/whole study) in wire cages in temperature-controlled rooms for fourteen days.

At the end of the study, our experimental animals in the groups were stopped from being fed, as they were free to drink water from 24:00 the day before they were sacrificed by cervical dislocation method. Brain, duodenum, liver, thyroid gland and testis tissues of rats were taken for biochemical and histopathological analysis and stored at -80.

Analysis of Oxidative Stress (MPO) and Antioxidant Enzymes (SOD) in Various Tissues

Biochemical kits were used for measuring: Myeloperoxidase; Rat MPO ELISA kit, (Sunred biological technology; Shangai, China) and Superoxide dismutaz; Rat SOD ELISA kit, (Sunred biological technology; Shangai, China)

Determination of Inflammatory Markers (TNF-α, IL-2, IL-6) in Brain, Duodenum, Heart, Liver, Thyroid and Testis Homogenate of Adult Male Rat

Serum cytokines; IL-2, IL-6 and TNF-α, were measured using a commercial available kits specific for rats (ELISA kits, Sunred biological technology; Shangai, China). Levels of IL-2 and TNF-α in serum samples were measured according to manufacturer's instructions.

Statistical Analysis

Descriptive statistics of quantitative variables in the groups were expressed as mean and standard error. The Shapiro-Wilk test was used to confirm the normality of the distributions of quantitative variables. The homogeneity of variances, which was a prerequisite for parametric tests, was checked with Levene's test. Differences between groups within the same parameter were checked with one-way ANOVA and Kruskal-Wallis test. Tukey HSD and Dunnett's post-hoc tests were used to determine the groups caused the significant difference. Groups with significant differences within the same parameter were indicated with different superscript letters. P<0.05 was considered significant in all statistical calculations. SPSS (version 20.0, SPSS Inc, Chicago) package program was used for statistical analysis of the data.

Results

In this study, 18 male Sprague Dawley rats were used. The experimental animals were divided into three groups. The groups were exposed to a comfort temperature, 30 °C, and 35 °C, respectively. At the end of the experimental procedure, inflammatory markers (IL-2, IL-6, and TNF-α) in the brain, duodenum, heart, liver, thyroid, and testis tissues; MPO as an oxidative stress marker; and SOD levels indicating antioxidant activity were determined. (Tables 1-3 and Figure 1).

Biochemical Results

Brain

As shown in Table 1 and Figure 1, heat exposure in the brain tissue resulted in a higher IL-6 level and SOD activity, and a lower TNF-α concentration in the HS2 group compared to the control group (p<0.05, Table 1 and Figure 1).

Duodenum

Compared to the control group, HS1 group duodenal IL-2 level was higher in rats exposed to heat, and HS2 group duodenal TNF-α concentration was higher compared to the control group as well (p<0.05, Table 1 and Figure 1).

Heart

As shown in Table 2 and Figure 1, IL-6 and MPO levels of the heart tissue of the HS2 group exposed to 35 °C temperature were higher than the control and HS1 groups (p<0.05).

Liver

Heat exposure in the liver resulted in decreased IL-2 levels compared to the control group (p<0.05). Hepatic IL-6 level increased in the HS2 group compared to the HS1 group (p<0.05, Table 2 and Figure 1).

Table 1. Effects of Heat Stress Exposure on Oxidant/Antioxidant and Inflammatory Biomarkers in Brain and Duodenal Tissues.

	Control	HS1 (30 °C)	HS2 (35 °C)	*p
Parameters **Brain**	Mean ± SEM	Mean ± SEM	Mean ± SEM	
IL-2	.2282±.0466	.2262±.0511	.2697±.0477	.778
TNF- α	.4694^{a}±.0250	.3794^{b} ±.0126	.4491^{ab}±.0170	**.014**
IL-6	.1853^{a}±.0175	.2348^{ab}±.0412	.3136^{b}±.0221	**.026**
MPO	.2568±.0314	.2351±.0337	.1906±.0044	.368
SOD	.1754^{a}±.0188	.2134^{ab}±.0406	.3044^{b}±.0424	**.045**
Duodenal				
IL-2	.1421^{a}±.0081	.2614^{b}±.0627	.1506^{ab}±.0135	**.044**
TNF- α	.1498^{a}±.0105	.2362^{ab}±.0396	.2603^{b}±.0346	**.042**
IL-6	.1897±.0115	.2432±.0432	.1899±.0220	.349
MPO	.2144±.0583	.2139±.0528	.2468±.0062	.763
SOD	.1443±.0138	.1514±.0089	.2122±.0360	.468

SEM: Standard error of mean, *p<0.05 is considered statistically significant. Bold texts are important; ^{a,b}: Means followed by different superscript letter in the same row are significantly different (p<0.05).
TNF: Tumor necrosis factor, MPO: Myeloperoxidase, SOD: Superoxide dismutase

Thyroid

As shown in Table 3 and Figure 1, no statistically significant change was observed in thyroid tissue IL-2, IL-6, TNF-α, MPO and SOD values at 30 °C and 35 °C exposure (p>0.05).

Testis

Exposure to heat stress in testicular tissue resulted in an elevation of IL-2 levels in the HS1 group compared to controls (p<0.05). Testicular concentrations of TNF-α were increased in both HS1 and HS2 groups relative to the control group (p<0.05), and SOD activity in testicular tissue also showed a marked increase compared to controls (p<0.05).

Discussion

HS is increasingly significant due to global warming (21,22). Exposure of the body to heat can cause different physio/pathological conditions. Behavioral and autonomic temperature-defense negative feedback mechanisms are used to maintain normal body temperature. Physiologically, successful activation of defense mechanisms results in temperature tolerance. With repeated, chronic heat exposure, tolerance intensifies, leading to heat acclimation. Heat-related diseases develop when the pathological effects of heat load are not prevented. Syndromes range from less severe such as heat syncope to severe forms such as fatal heatstroke (23) .

Table 2. Effect of heat stress exposure on liver and heart tissues oxidant/antioxidant and inflammatory biomarkers

	Control	HS1 (30 °C)	HS2 (35 °C)	*p
Liver	Mean ± SEM	Mean ± SEM	Mean ± SEM	
IL-2	.2881^{a}±.0046	.2116b±.0499	.2418^{ab}±.0044	.040
TNF- α	.4194±.0540	.4297±.0676	.3233±.0758	.481
IL-6	.2597^{ab}±.0457	.2116b±.0290	.3753^{a}±.0137	.027
MPO	.2395±.0387	.2225±.0456	.1506±.0205	.292
SOD	.1958±.0321	.1311±.0060	.1590±.0105	.068
Heart				
IL-2	.3942±.0105	.3050±.0570	.2440±.0642	.144
TNF- α	.5015±.0409	.4429±.0332	.3952±.0214	.113
IL-6	.2352^{a}±.0149	.3073^{a}±.0323	.3911^{b}±.0018	.004
MPO	.1900^{a}±.0046	.1799^{a} ±.0152	.3073^{b}±.0483	.017
SOD	.1807±.0133	.1400±.0124	.1934±.0258	.138

SEM: Standard error of mean, *p<0.05 is considered statistically significant. Bold texts are important; a,b: Means followed by different superscript letter in the same row are significantly different (p<0.05).
TNF: Tumor necrosis factor, MPO: Myeloperoxidase, SOD: Superoxide dismutase

Table 3. Effect of exposure to heat stress on oxidant/antioxidant and inflammatory biomarkers of thyroid and testicular tissue

	Control	HS1 (30 °C)	HS2 (35 °C)	*p
Parameters Thyroid gland	Mean ± SEM	Mean ± SEM	Mean ± SEM	
IL-2	.3038±.0687	.2093±.0529	.2422±.0673	.595
IL-6	.3312±.0700	.3327±.0577	.2889±.0319	.801
TNF- α	.3880±.1000	.3577±.0341	.2920±.0062	.619
MPO	.2911±.0710	.2870±.0482	.3392±.0033	.726
SOD	.1566±.0188	.1828±.0272	.2002±.0192	.441
Testicular tissue				
IL-2	.1729^{a} ±.0271	.2985^{b}±.0438	.2256^{ab}±.0159	**.045**
TNF- α	.2811^{a} ±.0152	.6000^{b}±.0303	.3512^{a}±.0340	.000
IL-6	.2073 ± .0251	.2929 ± .0375	.2955 ± .0082	.084
MPO	.2135±.0390	.2806±.0625	.3634±.0892	.309
SOD	.1276^{a} ±.0152	.1846^{ab} ±.0413	.2478^{b}±.0044	**.016**

SEM: Standard error of mean, *p<0.05 is considered statistically significant. Bold texts are important; ^{a,b}: Means followed by different superscript letter in the same row are significantly different (p<0.05)
TNF: Tumor necrosis factor, MPO: Myeloperoxidase, SOD: Superoxide dismutase

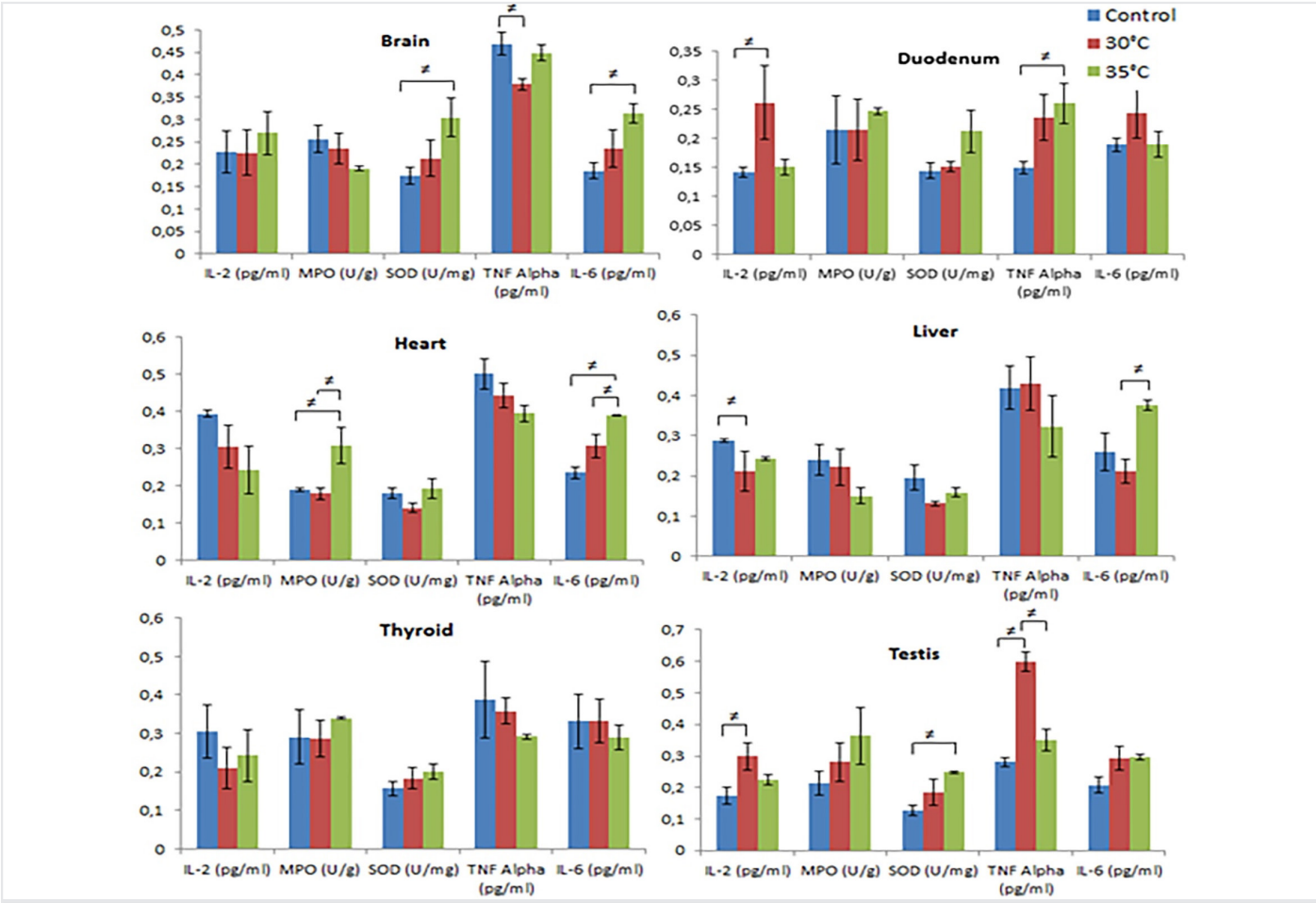

Figure 1. Effects of heat stress exposure on oxidant/antioxidant and inflammatory biomarkers across various tissues.

There are number of internal environment changes and systemic effects caused by HS in the organism as determined in the literature. However, our study determined the effects of high-temperature stress exposures, beyond the comfort temperature, on the oxidant system (MPO, SOD) and inflammation markers (IL-2, IL-6, TNF-α levels) in various tissues, supplementing existing literature (Tables 1-3 and Figure 1).

HS changes the physiology of all systems in the body with impaired redox homeostasis (24). MPO, secreted from activated polymorphonuclear leukocytes, increases OS by promoting free oxygen radical production.Therefore, excessive MPO production can damage tissues and organs (25). It was determined in our study that the heart tissue MPO level of the HS2 group was higher than that of the control group and HS1 group ($p<0.05$, Table 2 and Figure 1). This result shows that exposure to 35 °C HS increases the oxidant level associated with heart tissue leukocyte activation. In a study conducted by Horowitz et al. (26), the tissue damage caused by HS was associated with increased free radical production in animals exposed to high ambient temperature (42 or 43 °C). In another study, it was reported that chickens exposed to 36 °C for 8 hours a day showed a rapid increase in ROS production in mitochondria of duodenal, jejunal and ileal epithelial cells (27). An *in vitro* study with intestinal epithelial cells showed that exposure to 42 °C for 60 minutes increased ROS concentration and mitochondrial dysfunction and early apoptotic rates (28).

Free radicals produced continuously in the cell are destroyed by the antioxidant defense systems that are produced during normal metabolism in the body. Antioxidants basically prevent or delay cell damage by scavenging free radicals in the cell. Antioxidants can either be produced naturally in the body or obtained from external foods (29). SOD is the most important antioxidant defense system against ROS and superoxide anion radicals (30). When Table 1 and Table 3 were examined, it was seen that 35 °C temperature exposure increased the SOD activity of brain and testis tissues ($p<0.05$). The increase in the activity of SOD, an antioxidant enzyme, in brain and testicular tissues may be an antioxidant defense response to increased reactive oxygen intermediates.

Cytokines are intracellular peptides that act as immune system mediators. In both human and animal models, the levels of pro-inflammatory and anti-inflammatory cytokines increase in heat stroke (17). The inflammatory reaction associated with heatstroke includes activation of the humoral and cellular components of the immune system, as well as alterations in the production and/or suppression of numerous cytokines (31-

33). The findings of this study suggest that HS is associated with changes in proinflammatory cytokine levels. When the inflammatory responses of the tissues are examined; duodenum TNF-α concentration, heart and brain IL-6 levels increased, while brain TNF-α concentration and liver IL-2 levels decreased ($p< 0.05$). *Ex vivo* and *in vitro* studies characterizing the direct effects of heat have shown that it activates numerous pathways related to the physiological or cellular/biochemical axis (17,34). In a study by Helwig and Leon (35) using a mouse model of heat stroke, it was reported that the IL1 cytokine family played a role in the development of organ damage (spleen and liver). Another study showed that exposure to heat directly affected intestinal permeability and function The inflammatory response in animals exposed to mild to severe heat has the potential to impair nutrient absorption, gut health, and immunological status of the affected organism (34,36).

The potent inflammatory response to heatstroke increases after the end of HS and is intricately involved in both the damaging processes and the repair mechanisms activated during the healing phase. In survivors, the magnitude of this response decreases as time progresses, allowing a return to normal homeostasis. A stronger inflammatory response is often associated with poor prognosis and even death, indicating an imbalance in the immune system and causing a dysregulated inflammatory response (17). Consequently, HS can cause organ dysfunction associated with the accumulation of oxidants and the release of proinflammatory mediators. Future research should aim to elucidate the role of the immune inflammatory response in heat-stressed organisms. Nutritional and therapeutic interventions can prevent damage to organs due to HS and increase thermal tolerance to heat by reducing the accumulation of oxidants, but additional data are needed to support this theory.

Study Limitations

It is important to acknowledge the limitations of the current study. Because only male rats used in the experiments, these findings might not apply to female rats. Further studies that include different genders, ages, ete. are necessary. Future research should consider this difference.

Conclusion

As a result, exposure to high temperatures (30 °C or 35 °C) outside the room temperature of 24 °C, which is known as the comfort temperature, causes changes in the redox status of rats, in oxidant and antioxidant levels, and also in the levels of cytokines, known as immune system mediators. This indicates that exposure to high temperatures may lead to homeostasis changes in living organisms, resulting in deterioration of tissue and organ functions.

Ethics

Ethics Committee Approval: The approval to our study was granted by Atatürk University Local Ethical Committee for Animal Experiments with the decision number 7704040475-641.04-E.1900352247 (dated: December 31, 2019 and numbered: 2019/238).

Informed Consent: This study does not apply because it involves animal subjects.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: E.S., H.U., Design: E.S., H.U., Data Collection or Processing: E.S., H.U., Analysis or Interpretation: E.S., H.U., Literature Search: E.S., H.U., Writing: E.S., H.U.

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Review

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The Impact of Climate Change on Chronic Kidney Disease

İklim Değişikliğinin Kronik Böbrek Hastalığı Üzerindeki Etkisi

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ABSTRACT

Climate change problems like air pollution and global warming are assumed to be related to human activity. Global warming and air pollution are related issues. The state of health is assumed to be negatively impacted by these climatic changes, particularly in terms of the incidence and progression of chronic kidney disease. The aim of this review is to update physicians on how air pollution and global warming affect kidney disease.

Keywords: Climate change, chronic kidney disease, heat stroke, particulate matter

ÖZ

Hava kirliliği ve küresel ısınma gibi iklim değişikliği sorunlarının insan faaliyetleriyle ilgili olduğu varsayılmaktadır. Küresel ısınma ve hava kirliliği birbiriyle ilişkili konulardır. Sağlık durumunun, özellikle kronik böbrek hastalığı insidansı ve ilerlemesi açısından, bu iklim değişikliklerinden olumsuz etkilendiği varsayılmaktadır. Bu derlemenin amacı, hekimleri hava kirliliği ve küresel ısınmanın böbrek hastalığını nasıl etkilediği konusunda güncellemektir.

Anahtar Sözcükler: İklim değişikliği, kronik böbrek hastalığı, sıcak çarpması, partikül madde

Introduction

One of the biggest hazards to human health in the twenty-first century is climate warming, which is responsible for 12.6 million deaths in the world (1). Both kidney illness and climate change get worse over time. Those who repeatedly or extensively undergo dehydration insults from extreme heat are more likely to suffer from acute or chronic kidney problems. Particle pollution, a primary result of burning fossil fuels, may also be largely responsible for the prevalence of chronic kidney disease (CKD) and CKD-related pathology (2).

The UN Framework Convention on Climate Change defines climate change as a change of climate that is related directly or indirectly to human activity that modifies the composition of the global atmosphere in addition to natural climate variability (3). Climate change poses a dilemma that imperils the continuation of life as we know it on Earth. Recognizably, according to the Intergovernmental Panel on Climate Change (IPCC), human activity has caused climate warming at an unusual tempo in the last 2000 years (4). If emissions continue at their current rate, the IPCC estimates that globally the temperatures will rise by 2-3.5 degrees Celsius by the end of the century (4).

The effects of climate change are particularly harmful to kidney health because environmental issues make kidney diseases worse. However, dialysis therapy has a significant environmental impact due to a variety of aspects, including energy and water use, greenhouse gas emissions, and waste production (5).

Despite numerous international climate agreements, the world's reactions are woefully insufficient, and the nephrological community's involvement appears to be lacking (5).

Climate Change-Related Kidney Disorders

People with kidney illness are more vulnerable to the direct health effects of climate change as well as to disruptions in the healthcare system during natural disasters, which exacerbates the variety of negative effects of climate warming (6). Climate change effects like heat exposure and volume depletion are risk factors for nephrolithiasis, acute kidney injury (AKI) as well as CKD in South America and abroad (Mesoamerican nephropathy) (7).

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Low air quality has a negative impact on the progression of CKD. In addition, due to climate warming, changes in the landscape caused by precipitation, and human behavior that increases vector-human contact, vector-borne diseases continue to be major causes of kidney disease in low-income nations and are spreading throughout the world (8).

Heat stress as a cause of kidney disorders

In recent studies, CKD epidemics have been reported in several high-temperature places of the world, mainly affecting individuals who perform physical work in sweltering temperatures. (9) The disease is more prevalent in Central America's hotter regions due to heat stress (10), which has given rise to the theory that kidney disorders may be caused by global warming (11). In fact, a study revealed that working in sugarcane fields was linked to higher humidity since there were cane present and El Nino events (12). Also, several studies in South America have shown that repeated AKI from heatstroke is increasing the incidence of CKD in sugarcane workers (13-15). The majority of cases show no symptoms, but some patients exhibit fever, leukocytosis, leukocyturia, and AKI, which may necessitate hospitalization (16).

Increased body temperatures, the activation of the polyol-fructokinase pathway by hyperosmolarity, and the long-term effects of vasopressin on tubular and glomerular injury are probably the mechanism of AKI (17). Also, according to different studies, heat, volume depletion, and increased uric acid serum levels due to exercise-induced rhabdomyolysis result in concentrated and acidic urine, which can cause tubular injury, nephrolithiasis, and urinary tract infection (18-20). Rehydrating with soft drinks also carries the risk of AKI because they contain fructose, which when metabolized by the kidneys causes tubular damage, inflammation, and oxidative stress (21).

Heat stress nephropathy is now being documented worldwide, especially in hot agricultural communities, which is concerning since it can lead to an epidemic of CKD (22,23).

Vector-Borne Diseases and Kidney

In warm areas, acute febrile infections from vector-borne diseases are a major contributor to AKI. The most frequent diseases that occur in warmer climates are caused by the zika virus, malaria, and dengue. Mosquitoes, especially female ones, which are mostly to blame for vector-borne diseases, eat more often and lay more eggs in warmer climates (24). The mortality rate for patients with malaria increases by 45% when AKI is present (25). Even though the information on AKI caused by dengue is scarcer and more inconsistent, rates that have been documented in patients who have needed hospitalization are relatively high, with fatality rates of 9% to 25% (26). Another mosquito-borne virus, Zika, may become more dangerous to people as a result of climate warming. Often asymptomatic or resulting in a mild febrile viral disease, the infection can result in fetus malformation, such as microcephaly (27). Travelers with immunosuppressed conditions, such as those with kidney disease or who are receiving dialysis, and transplant patients have recently been warned to take vigilance (27).

Particulate Matters and Kidney

One of the main contributors to the burden of diseases worldwide is considered to be air pollution (28). The principal component of air pollution that has the greatest detrimental impact on human health is particulate matter (PM), which predominantly consists of solid particles produced during the combustion of coal, gasoline, and diesel fuels (29). Other elements of environmental air pollution may include differently sized particulates (e.g., $PM_{2.5}$, which has a diameter of 2.5 μm, and $PM_{2.5-10}$), gaseous pollutants (e.g., nitrogen dioxide, carbon monoxide, sulphur dioxide, and ozone), and heavy metals (cadmium, lead, and mercury) (30).

It is commonly assumed that particulate matter, especially $PM_{2.5}$, has a negative impact on the onset and progression of cardiovascular disease due to the high risk of vascular dysfunction, like inflammation and atherosclerosis (31,32). The kidney, which is composed of arteries and arterioles, may potentially be vulnerable to PM-related atherosclerosis (31). A new risk factor for CKD that is getting increasing attention currently is air pollution (33), which is in addition to traditional risk factors for the development of kidney diseases such as hypertension, diabetes, ethnicity, age, smoking, episodes of AKI, use of analgesic drugs, and genetic factors (34,35). In a local cohort study where 669 older men were conducted, Mehta et al. (36) discovered that every 2.1 $\mu g/m^3$ increase in $PM_{2.5}$ exposure was linked to a 1.87 mL/min/1.73 m^2 decrease in eGFR and an additional yearly impairment in kidney function of 0.60 mL/min/1.73 m^2. According to a different study by Xu et al. (37), membranous nephropathy risk was elevated by prolonged exposure to high $PM_{2.5}$ concentrations. According to a cohort study, conducted on more than 2 million US veterans without a history of kidney disease, chronic exposure to PM and gaseous pollutants is linked to an elevated risk of new-onset and progression of CKD, and development of kidney failure which requires renal replacement therapy (34). The risk is increased by 26-28% for every 10 $\mu g/m^3$ rise in $PM_{2.5}$ concentration (34).

Arsenic

The occurrence of kidney damage and the start of hypertension may both be influenced by exposure to arsenic (As) in the environment, at work, and in an individual's diet (38,39). A study conducted in Taiwan showed a significant relationship between urinary As and the incidence of CKD. It was shown that high levels of urine As quadrupled the chance of developing CKD (40). Acute As exposure to the kidney can cause hypercalciuria, albuminuria, nephrocalcinosis, and necrosis of the kidney papillae, as well as tubulointerstitial nephritis and acute tubular necrosis (41,42).

Cadmium

Another common nephrotoxic environmental contaminant is cadmium (Cd). Diet and smoking are the main sources of Cd exposure. Since Cd directly damages the kidneys, it can result in polyuria, tubular damage, Fanconi syndrome, as well as progressive reduction of eGFR (43). The idea that chronic

Cd exposure is thought to hasten the progressive reduction of eGFR is supported by a variety of experimental research (44,45). Proteinuria is the most common complication (46). Megalin and cubilin, which promote the endocytosis of filtered proteins along the proximal tubule, have been linked to proteinuria (47,48). The prevalence of kidney stones also rises in people who are persistently exposed to or receive higher doses of Cd, probably as a result of the elevated calcium concentration in urine (38).

Lead

The primary effects of lead (Pb) exposure on kidney cells are inflammation and mitochondrial oxidative stress (38). Exposure to low levels of Pb results in glomerular hypertrophy (38). Fanconi syndrome is caused by acute Pb exposure and tubulointerstitial nephritis from long-term Pb exposure (49). Different studies conducted in different countries showed a positive correlation between Pd exposure and serum creatinine concentration (50,51).

Mercury

Mercury (Hg) has also been linked to the development of CKD (52). Endoplasmic reticulum dilatation, transformed mitochondrial structure, and nuclear pyknosis are all results of short-term exposure (53). Microvilli start to disappear after 12 hours, and cell death is accompanied by rupture of the plasma membrane and cell separation from the basement membrane (54). Glomerular damage can also result from long-term exposure to Hg substances (38). A study that included 272 participants with CKD and 272 controls who were matched for age, sex, and area revealed that exposure to Hg was independently linked to a higher probability of developing CKD (55).

Tobacco

Another air contaminant that is hazardous to kidneys is tobacco. There are various theories that explain various mechanisms related to CKD. In healthy persons, smoking has been linked to microalbuminuria and idiopathic nodular glomerulosclerosis, and in those with CKD, especially with diabetic nephropathy (DN), it has been linked to more heavy proteinuria (56,57). In a study where 926 cases of CKD and 998 controls participated, an association between smoking and glomerulonephritis and nephrosclerosis was discovered (58). Smoking accelerated the development of DN and nephroangiosclerosis (58,59). Endothelial dysfunction, intimal hyperplasia, and atherosclerosis of small and large vessels are all effects of tobacco (57). Ingredients in tobacco cause glomerulosclerosis, tubulointerstitial fibrosis, and mesangial proliferation in the kidney (60). Particularly, nicotine increases the formation of extracellular matrix in human mesangial cells (61) and acrolein causes kidney cell apoptosis and the generation of reactive oxygen species (ROS) (62). Another component of tobacco that negatively affects CKD is Cd. Smokers' serum Cd concentrations are 4- to 5-times greater than non-smokers', and their kidney Cd concentrations are 2- to 3-times higher (63).

An experimental study suggested that mechanisms for smoking-induced kidney injury included increased sympathetic activity which led to hypertension and increased intraglomerular capillary pressure (64). It was shown that the incidence of kidney function loss was greater in current smokers than in non-smokers (65).

In addition to these results, cigarette use has also been linked to proteinuria in people with and without CKD (66-68). Proteinuria was discovered in 4.6% of current smokers and 1.5% of non-smokers among a population selected from a chemical factory in Japan (68). In a meta-analysis among smokers with type 1 DM or type 2 DM compared to non-smokers, the incidence rate of DN was greater (69). Also, the study indicated that smoking posed the greatest risk for macroalbuminuria, most likely over a long period of time (69). To assess smoking exposure, measurements of the nicotine metabolite cotinine and creatinine levels in serum, as well as the albumin/creatinine ratio were evaluated in a study conducted in Turkey (70). Serum cotinine concentrations and the urinary albumin-creatinine ratio were both greater in current and passive smokers than in controls, although creatinine blood concentrations were higher in current smokers (70).

Traffic air pollution

Another type of air pollution is that caused by traffic. In a study in Taipei city, the authors came to the conclusion that 1-year exposures to air pollution from traffic, especially to $PM_{2,5}$ and PM_{10}, were linked to lower eGFR, a higher prevalence, and incidence of CKD (71). In another study conducted in Runcorn, UK, the author found that compared to a control population residing distant from industrial facilities, those who lived close to industrial facilities had an increased mortality rate from CKD (72).

The effect of kidney disease on the environment

The medical industry has a significant environmental impact because of the amount of water and energy used in manufacturing, interventions, and waste production (73). Nature is in danger due to the pharmaceutical sector's large-scale emissions of greenhouse gases and pollutants (74). Non-etheless, dialysis involves a heavier strain compared to other therapeutic modalities. There is no doubt that producing plastic, which is a crucial element of dialyzers and dialysis equipment, needs a significant quantity of chemicals, energy, and water (75). Moreover, each dialysis session uses large amounts of drinkable water, including reverse osmosis water and dialysate generation (75). With a lot of such units around the world, the typical unit's water use can easily reach one million liters per year (75). Numerous factors contribute to the extensive production of greenhouse gases and pollutants, including the manufacturing of filters, machines, and other consumables, dialysate production and heating, monitoring, lighting, and climatization of the unit, as well as the transport of materials and patients (76,77). Discarding auxiliary resources increases the waste problem even more (gloves, protective clothing, food packages, and drinking cups for meals provided during dialysis, drug wrappings, and containers) (78). However, there is no data comparing the overall ecological burden of peritoneal dialysis and hemodialysis (HD) techniques. According to one investigation, transplanting had a better environmental impact compared to dialysis modalities (79). Although home

dialysis is frequently thought of as being more environmentally than other modalities due to the lower water consumption of the treatment, this is likely largely countered by the water and energy required to create a large number of plastic dialysate bags, dialysate, and transport those bags (77,79).

Conclusion

In conclusion, climate change has a big impact on people's health. Dehydration, elevated serum uric acid levels, and hyperosmolarity induced by heat stroke can result in AKI, which can eventually result in CKD. Due to the dysregulation of renal hemodynamics, oxidative stress, and inflammatory response, air pollution, an increased level of varied-size PM and heavy metals may also result in AKI. People need to be educated about maintaining a low-carbon lifestyle and stopping smoking.

Ethics

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: L.S., R.K., Design: L.S., R.K., Data Collection or Processing: L.S., R.K., Analysis or Interpretation: L.S., R.K., Literature Search: L.S., R.K., Writing: L.S., R.K.

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Review

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Phytotherapy in Obesity: Is It Necessary to Have Surgery?

Obezitede Fitoterapi, Ameliyat Olmak Şart mı?

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ABSTRACT

The prevalence of obesity, which is defined by the World Health Organization as abnormal or excessive fat accumulation in the body that impairs health, is increasing day by day. In addition to behavioral therapy aimed at changing the individual's lifestyle based on the strategies developed against the disease, diet therapy, exercise, medical nutrition therapy, pharmacological and, as a last resort, surgical treatment are recommended. The effect of methods other than surgical treatment on weight loss is slow. For this reason, many obese patients prefer obesity surgery to lose weight quickly, but these methods have many complications such as weight regain, tachycardia, fistula, bleeding, herniation, anastomotic stenosis, gastric erosion, small bowel obstructions, deep vein thrombosis and pulmonary embolism. Post-surgical weight regain and complications have recently led to new searches, and the use of medical nutrition and phytotherapy products has again come to the fore as hope. Phytotherapy products can also be used alone or in combination with other methods. Natural anti-obesity products have functional ingredients such as phytochemicals, polyphenols, flavonoids and phytosterols. There are many natural products used in this field and therefore there are different classifications. Phytotherapeutics are classified according to their effectiveness as those that increase fat burning and stimulate metabolism, suppress appetite, create a feeling of satiety, control blood sugar and insulin, inhibit the absorption of carbohydrates and fats, and inhibit inflammation. However, more clinical research is needed to elucidate the antiobesity effectiveness and mechanism of action of natural products. The risks and side effects of the method to be chosen in obesity treatment should be discussed with the patient. Recommendations to the patient should be given after a multidisciplinary evaluation. Treatment should be started with the most appropriate and least risky method for the patient's current condition. It should be explained to the patient that it is most likely that he/she will lose weight with one of these methods, but that the important thing is to maintain his/her weight through behavioral changes.

Keywords: Obesity, phytotherapy, surgery, lifestyle change, diet

ÖZ

Dünya Sağlık Örgütü tarafından, vücutta sağlığı bozacak ölçüde anormal veya aşırı yağ birikmesi olarak tanımlanan obezitenin prevalansı her geçen gün artmaktadır. Hastalığa karşı geliştirilen stratejiler temelinde bireyin yaşam tarzını değiştirmeye yönelik olan davranış terapisinin yanında, diyet tedavisi, egzersiz, tıbbi beslenme tedavisi, farmakolojik ve son çare olarak ise cerrahi tedaviyi önermektedir. Cerrahi tedavi dışındaki yöntemlerin kilo kaybı üzerindeki etkisi yavaştır. Bu yüzden obez hastaların birçoğu hızlı kilo vermek adına obezite cerrahisi yöntemlerini tercih etmektedir fakat; bu yöntemeler başta kilo geri kazanımı olmak üzere taşikardi, fistül, kanama, fıtıklaşma, anastomoz darlığı, gastrik erozyon, ince bağırsak tıkanıklıkları, derin ven trombozu ve pulmoner emboli gibi birçok komplikasyonu da beraberinde getirmektedir. Cerrahi sonrası kilo alımı ve yaşanan komplikasyonlar son zamanlarda yeni arayışlara yol açmış ve tıbbi beslenme ve fitoterapi ürünlerinin kullanımı yeniden bir ümit olarak gündeme gelmiştir. Fitoterapi ürünleri tek başına ya da diğer yöntemlerle birlikte kullanılabilme özelliğine de sahiptir. Doğal obezite karşıtı ürünler; fitokimyasallar, polifenoller, flavonoidler ve fitosteroller gibi fonksiyonel içeriklere sahiptir. Bu alanda kullanılan birçok doğal ürün bulunmaktadır ve bu sebeple farklı sınıflamalar mevcuttur. Fitoterapötikler, etkinliğine göre; yağ yakımını artıran ve metabolizmayı uyaranlar, iştahı baskılayanlar, tokluk hissi yaratanlar, kan şekerini ve insülini kontrol edenler, karbonhidrat ve yağların absorbsiyonunu inhibe edenler, inflamasyonu inhibe edenler şeklindeki sınıflamaya tabii tutulmaktadır. Fakat yine de doğal ürünlerin antiobezite etkinliğini ve etki mekanizmasını aydınlatmak için daha fazla klinik araştırmaya ihtiyaç vardır. Obezite tedavisinde seçilecek yöntemin riskleri ve yan etkileri hasta ile tartışılmalıdır. Hastaya öneriler multidisipliner bir değerlendirmeden sonra verilmelidir. Hastanın mevcut durumuna en uygun ve en az riskli yöntem ile tedaviye başlanmalıdır. Hastanın bu yöntemlerden biri ile zayıflamasının büyük ihtimalle sağlanacağını ama önemli olanın davranış değişikliği ile zayıf kalmanın sürdürülmesi olduğu anlatılmalıdır.

Anahtar Sözcükler: Obezite, fitoterapi, ameliyat, yaşam tarzı değişikliği, diyet

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WHAT IS OBESITY?

Many definitions of obesity have been made to date. According to the World Health Organization, obesity is abnormal or excessive fat accumulation in the body that impairs health (1). The question of whether obesity is a disease or a condition resulting from a personal choice and lifestyle has not been answered for many years. It is a complex condition involving social, biological and psychosocial factors, and its prevalence is increasing worldwide. A sedentary lifestyle and high-calorie diet, hereditary and hormonal factors, spiritual-psychological reasons, age and gender-related reasons seem to be the most important factors in the development of obesity.

According to the data announced by the World Obesity Federation in March 2023, the number of overweight and obese adults over the age of 20, which was 813 million, was estimated to be 1 billion in 2025. Overweight and obesity are the fifth leading risk for global deaths. At least 2.8 million adults die each year as a result of being overweight or obese. Additionally, 44% of the burden of diabetes, 23% of the burden of ischemic heart disease, and 7% to 41% of the burden of certain cancers are attributable to overweight and obesity (2).

Global anti-obesity strategies focus on diet and lifestyle changes to slow the development of obesity. In the treatment of obesity, behavioral modification therapy, exercise, medical nutrition therapy, pharmacological and, as a last resort, surgical treatment can be applied.

Bracketing and personal planning have an important place in the fight against obesity. All evaluations regarding the cause of obesity are made multifaceted and the solution is approached gradually after the cause is corrected. At the end of all treatment applications, the expected goal is to create behavioral change and ensure that it is permanent.

1. Lifestyle Change

Lifestyle change is the cornerstone of obesity management. The purpose of treating obesity with behavior modification therapy is to raise awareness and change the lifestyle that the patient has adopted, such as physical activity and nutrition habits, which cause excessive weight gain, and to provide a behavioral model that will keep him/her away from obesity. Behavior changes should include individual efforts such as nutrition education, regulation of the number and quantity of meals, doing what is necessary for a healthy life, switching to an active lifestyle with exercising, avoiding sugary drinks, and eliminating the causes of obesity, as well as government policies such as banning advertisements of foods that encourage obesity, producing healthy products, and changing social habits through regulations in laws (3).

2. Diet Therapy

Weight loss can be achieved through a net kilocalorie (energy unit) deficit. The estimated energy expenditure per kilogram of adult body weight is approximately 22 kcal. Reducing intake to create a net energy deficit can be achieved in various ways.

2.1. Macronutrient Composition

The three basic dietary macronutrients are fat, carbohydrates, and protein. Fat is the least filling, most easily absorbed, and most calorie-dense macronutrient, making it the most attractive target for weight loss intervention. A meta-analysis of low-fat diets shows significant weight loss compared to baseline intake but no weight loss compared to other dieting methods, including high-fat diets (4). Low-carb diets (LCDs) produce rapid results with greater initial weight loss (up to 3.3 kg in 6 months) compared to low-fat diets. However, most of this has been attributed to the loss of glycogen stores and water, reaching 1-2 kg in the first 14 days, after which the rate of weight loss slows down. Protein is very filling and is used in high-protein diets to reduce the consumption of other less filling, energy-dense nutrients. However, recent meta-analyses have concluded that these proteins have either no effect or a minor effect of questionable benefit on body weight (5).

2.2. Calorie Restriction

Another approach to achieving a net energy deficit is to directly limit calorie intake. Low and very low calorie diets (LCD: 800-1,600 kcal/day and VLCD: <800 kcal/day) limit energy intake (6). VLCDs provide superior short-term weight loss compared to LCDs (-16.1 kg vs -9.7 kg, respectively). Weight loss with VLCD is achieved primarily through total body fat loss (7.8% reduction in total body fat in 6 months). However, the long-term benefits of VLCDs are less clear, with higher rebound weight gain (61% versus 41%, respectively). In a systematic review by Franz et al., weight loss with VLCDs was found as 17.9 kg (16%) at six months, after which the weight loss began to decrease (-10.9 kg or -10% at 12 months and -5.6 kg or -5% at 36 months) (7).

2.3. Meal Replacement

Full or partial meal replacement (PMR) includes nutritionally filling but low-calorie meals for daily meals and recommends restricting calorie intake. Meal replacement may lead to greater weight loss than traditional calorie restriction. A meta-analysis of six studies by Heymsfield et al. supported this view. PMR provided greater weight loss in 3 months (-2.54 kg) and 1 year (-2.63 kg) with lower effort (8). Additionally, although subjects who applied PMR gained more weight over the long term compared to conventional diets, overall weight loss remained greater (-7.8% vs. -5.9% at 40 weeks).

However, the effect of behavioral exercise on weight loss is slow and is not suitable for obese patients with cardiovascular diseases. Recently, in nutrition research, great attention has been paid to the use of natural products in the fight against obesity.

3. Pharmacotherapy

Pharmacological treatments are recommended to maintain weight loss in addition to a low-calorie diet and optimal physical exercise. However, the pharmacological options available are very limited. Additionally, if less than 5% weight loss is achieved while using the medication, the treatment should be discontinued in the 3rd month (9). The main drugs used for this purpose are:

3.1. Orlistat

Orlistat irreversibly inhibits pancreatic lipases, which break down dietary fat into absorbable free fatty acids, preventing the absorption of up to 32% of ingested fats and allowing these fats to be excreted in the feces. To reduce side effects, patients are advised to follow a low-fat diet with medications taken during or up to 1 hour after meals. A meta-analysis of 33 randomized controlled studies showed an average reduction in body weight of 2.12 kg, although the average treatment duration varied between 2 months and 3 years (10).

3.2. Liraglutide (Saxenda®)

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist administered subcutaneously once daily. GLP-1 is an incretin hormone that is released from the gastrointestinal (GI) tract in response to glucose and fat intake and acts both peripherally and centrally. In other words, it both changes glucose homeostasis by slowing down absorption from the GI system and suppresses appetite (11). GLP-1 treatment results in an average weight reduction of 3.2 kg and improvement in glycemic control (1% reduction in HbA1c), cholesterol level and blood pressure.

3.3. Naltrexone/bupropion (Mysimba®)

Naltrexone/bupropion is a fixed-dose combination medication often prescribed in addition to diet and lifestyle changes, but is not currently recommended by healthcare organizations because the long-term effectiveness of the medication is unknown (12). In the multicenter, randomized, double-blind, placebo-controlled phase 3 study, the average change in body weight was determined to be -6.1% in 1,742 patients, while this rate was observed to be -1.3% in the placebo group (13).

Every drug causing weight loss has its own risks, so the doctor needs to fully understand the drug's contraindications and the differences between obese individuals. More importantly, long-term studies are needed to determine whether weight loss with medication will cause side effects.

4. Exercise

Current guidelines recommend at least 150 minutes of moderate-intensity or 75 minutes of high-intensity aerobic exercise per week and training involving all major muscle groups at least twice per week. For patients wishing to maintain weight loss, high levels of exercise (225-420 minutes/week of moderate intensity exercise) provided better weight control compared to lower levels (<150 minutes/week) (14). Although significant weight loss can be easily achieved, 80% of individuals are unable to maintain weight loss. Potential reasons for the high rate of WR after weight loss include increases in appetite hormones (e.g., ghrelin), decreases in anorexigenic hormones (e.g., leptin, glucagon-like peptide-1), decreased compliance with self-monitoring/weighing habits, and decreased resting metabolism with weight loss (15).

Exercise therapy should be prepared individually. In severely obese people, factors such as cardiovascular problems, joint problems caused by the pressure of excessive weight, and respiratory problems should be taken into consideration, and the type and level of exercise to be chosen should be according to the person's capacity.

5. Intragastric Balloon

Intragastric balloon (IGB) has been used since 1985 and very good results can be obtained. The balloon, which is usually placed endoscopically, is filled with saline and remains in the stomach for 6 months. IGB is an alternative option for weight loss in patients who refuse or are unsuitable for bariatric surgery. A Cochrane review concluded that there was little data to support its effectiveness for weight loss compared with traditional medical management (16). If the change in eating habits cannot be achieved permanently, weight may be regained after the balloon is removed.

6. Bariatric Surgery

Surgical treatment has become very popular recently. BS is often an effective therapeutic option for weight loss in people with severe obesity as well as for reducing diabetes in patients with low body mass index.

6.1. Laparoscopic Adjustable Gastric Band (LABG)

An inflatable silicone band is placed on the upper part of the stomach to narrow its lumen, restricting the passage of food and creating a small proximal gastric pouch that limits the amount of food that can be swallowed. The patency of the band, and therefore the degree of constriction, can also be adjusted by injecting fluid through a subcutaneous port. Major complications include band slippage (7.9%) and erosion (<1%) (17). Its use has decreased significantly due to recent complications.

6.2. Sleeve Gastrectomy

During sleeve gastrectomy (SG), 80% of the stomach is removed, leaving a narrow middle section. The reduced-sized stomach has lower mobility and restricts the volume of food passing

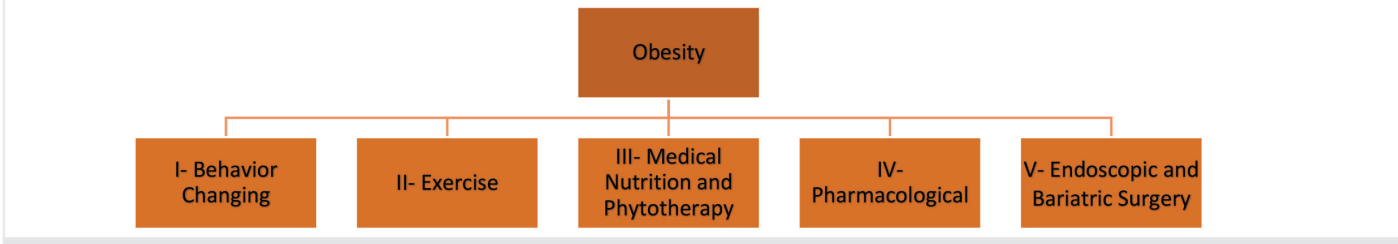

Figure 1. Stepped-care in obesity treatment

Table 1. Five-year follow-up data in laparoscopic sleeve gastrectomy surgery (26)

	Presurgery	Follow-up Year 1	Follow-up Year 2	Follow-up Year 3	Follow-up Year 4	Follow-up Year 5
Number of patients	N=140	N=123	N=99	N=77	N=52	N=44
Body weight (kg)	112.3±20.0	83.1±17.0	84.5±18.6	86.8±18.8	91.0±20.5	89.1±18.3
Rates of patients with successful weight loss (% EWL >50%)		79.2%	71.7%	58.4%	55.8%	54.5%
Rates of patients with unsuccessful weight loss (% EWL <30%)		7.3%	9.1%	13.0%	25.0%	22.7%
Weight regain (% REWL >25%)		--	1.0%	11.6%	19.2%	29.5%

REWL: , EWL: ,

Table 2. Weight gain data after laparoscopic sleeve gastrectomy (27)

	Follow-up duration 33 months
Total number of patients N=110	14 kg (12.7%)
Weight regained	

through it, thus limiting calorie intake. SG is usually performed laparoscopically and can provide up to 70% weight loss within 1 year, which is maintained for at least up to 3 years (18). It is the most commonly used method today.

6.3. Roux-en-Y Gastric Bypass

In Roux-en-Y gastric by-pass (RYGB), the stomach is divided from the upper part to create a small proximal gastric pouch. The small intestine is also separated at the jejunal level, where the distal part of the intestine is connected to the new gastric pouch. As a result, the digested food passes through the lesser sac and directly into the distal part of the small intestine, thus bypassing the proximal part and limiting absorption. The middle part of the cut intestine, the distal part of the stomach, and the proximal part of the small intestine are reconnected to the small intestine further down, allowing digestive enzymes to mix with the more distally digested food. RYGB is most often performed laparoscopically and provides an estimated 73% weight loss within 1 year. Serious complications include anastomotic leaks (3-5%) and internal bowel herniation (3.1%), which has the potential to lead to intestinal obstruction and perforation.

6.4. Biliopancreatic Diversion with Duodenal Switch

Biliopancreatic diversion with duodenal switch (BPD-DS) is a two-stage, open or laparoscopic procedure and is usually irreversible. First, a SG-like gastrectomy is performed by leaving a tube-shaped pouch. Secondly, the small intestine is cut in two places; proximally just after the pylorus and distally approximately 250 cm before the ileocecal valve. The distal small intestine is elevated and anastomosed to the duodenum. The distal end of the middle piece is then anastomosed to the small intestine approximately 100 cm before the ileocecal valve. Although mortality rates remain low (<1%), BPD-DS is a more complex procedure and is associated with perioperative anastomotic leaks (3-4%) and splenectomy (<1%), and subsequent malnutrition (4%), internal herniation, and small bowel obstruction. It has complications such as (2-7%) (19).

6.5. Complications of bariatric surgery

6.5.1. Weight regain after surgery

Bariatric surgery (BS) is currently the most effective intervention for severe obesity. Unfortunately, patients experience some weight regain (WR) after reaching their lowest weight. Approximately 20-25% of patients struggle with significant WR after BS. Similarly, suboptimal weight loss (SWL) (patients' weight loss <50%) is the most common reason they undergo revisional BS.

Although some researchers have proposed behavioral and biological mechanisms for WR (20), preoperative factors that predispose patients to significant WR remain unclear. Additionally, it is important to note that WR is associated with deterioration of quality of life and recurrence or worsening of obesity-related comorbidities such as hypertension and type 2 diabetes (T2D), which require close monitoring and appropriate management. Additionally, revisional BS performed to manage WR/SWL may result in higher complication and mortality rates compared to primary BS (21). Basic studies focusing on long-term outcomes after BS show that patients generally regain 5% to 10% of their total weight loss within the first decade (22).

WR is defined as progressive weight gain that occurs after initially successful weight loss (defined as extreme weight loss, >50%) has been achieved. Despite the lack of a standardized definition of WR and poor reporting of its clinical significance, according to the results of a study conducted on 1,406 patients, it was reported that the rates of WR ranged between 44% and 87% five years after RYGB. Moreover, the percentage of maximum weight loss, progression of T2D and hypertension, decreased quality of life, and decreased satisfaction with surgery are observed (23).

In a randomized prospective multicenter Swedish study, 10 years after laparoscopic adjustable gastric banding, patients regained 38% of the maximum weight they lost in 1 year (24), and in a long-term follow-up of more than 7 years, patients lost weight after laparoscopic SG. It was stated that the recovery rate was 27.8% (range 14-37) (25). In the light of data obtained from

studies conducted over the years, the tables for WR are presented below.

Publications in BS are largely based on evidences from randomized clinical trials with follow-up of only 1 to 3 years. The evidence includes single-site studies with small sample sizes, inadequate follow-up (>1 year), and lack of non-surgical comparison groups (29). Little is known about long-term (>5 years) maintenance of weight loss after BS. These may be due to factors associated with weight regain, study participant discontinuation, and loss to follow-up, which may lead to an inaccurately optimistic conclusion regarding the effectiveness of BS-induced weight loss when follow-up is not completed (less than 80%).

Despite the lack of quality long-term studies, available evidence suggests that the benefits of BS are not universal. Weight gain and recurrence of diabetes may occur in a significant proportion of patients (30). It is estimated that 10% to 30% of patients undergoing BS experience suboptimal weight loss. Indeed, SWL and WR are key factors associated with diabetes relapse, which may occur in 20-30% of patients who achieve remission 5 years after BS. Additionally, a proportion of patients undergoing BS also experience decreased recovery from other comorbidities (13%, 11%, and 4% of T2DM, hypertension, and LDL-cholesterol patients, respectively, after 6 years). However, the lack of high-quality long-term data makes it difficult to predict effects on many comorbidities.

In addition, all bariatric procedures affect nutritional intake and can also have an impact on the absorption of micro- and macronutrients, especially procedures that affect absorption (RYGB, SG, BPD-DS). Most patients will require lifelong nutritional supplements as well as a balanced diet.

It is also known that surgical treatment has effects on the psychology of patients. An increase in harmful behavior and suicide risk has been reported in patients after BS, and although the biological and behavioral mechanisms behind this are unclear, possible hypotheses include changes in the absorption of drugs, imbalances in peptides, hormones, and glucose. There is also evidence of the development of postoperative eating disorders (such as anorexia nervosa and bulimia nervosa), which may occur as a result of the dramatic changes in eating patterns specific to BS (31). Patients undergoing BS should be counseled regarding potential nutritional disorders.

6.5.2. Other Complications

The increasing prevalence of obesity has also led to an increase in the number of bariatric procedures. As a result, there is an increase in the complications of patients undergoing surgery. Complications encountered in patients can be classified in various ways. These include dumping syndrome, tachycardia, fistula, bleeding, herniation, anastomotic stenosis, gastric erosion, small bowel obstructions, deep vein thrombosis and pulmonary embolism, post-operative pneumonia, complications due to malnutrition, hepatobiliary complications, gastric ulcer, intestinal-related symptoms, mesenteric vein or portal system thrombosis and neurological complications (32).

The high side effects of pharmacological and bariatric surgical treatments and the inability to make regular lifestyle changes and exercise practices have led physicians to search for new approaches in obesity treatment. In this context, the use of medical nutrition treatments and phytotherapy products has recently become the focus of discussions. In addition, phytotherapy products have attracted attention with their ability to be used alone or in combination with other methods.

7. Medical Nutrition and Phytotherapy in Obesity

Phytotherapy is used alone or in support of drug treatment in many diseases. Interest in phytotherapy products is increasing day by day. There are many herbal products on the market in the form of dry extracts, concentrated plant extracts, tablets and capsules containing herbal mixtures, aqueous-alcoholic extracts and tinctures. However, information about the effectiveness, reliability and quality of most of the products used by patients for this purpose is insufficient. However, the mechanism of the active ingredients in the plant used, the bioactive phytochemicals responsible for the anti-obesity activity and the standardized dose should be known. There should be no side effects if possible, and possible side effects should be described.

When looking at the functional ingredients in natural anti-obesity products, it appears that the consumption of phytochemicals can greatly contribute to biological effects. The mechanisms of action of phytochemicals are preventing the proliferation of precursor cells, increasing the effect of apoptosis, inhibition of pancreatic lipase activity and increase in energy expenditure (33).

Polyphenols are functional compounds with anti-carcinogenic, anti-oxidant, anti-bacterial and anti-viral activities. In the last two decades, polyphenols have been reported to have beneficial effects against obesity. For example, dietary polyphenols can regulate adipocyte metabolism to inhibit the growth of adipose tissue (34).

Flavonoids are abundant in nature. It has been proven that it has positive effects against obesity. They can modulate a number of cell signaling pathways to influence carbohydrate digestion, fat accumulation, rate of insulin release, and glucose uptake in insulin-sensitive tissues.

Phytosterols, which include plant-derived sterols and stanols, are compounds structurally similar to cholesterol. They are found in high concentrations in vegetable oils such as corn, soybean and sunflower oil. It has been proven that plant stanols and sterols can block intestinal fatty acid absorption and reduce body weight gain in animal tests (35).

Being natural (safe, harmless), having few side effects, thinking that professional help is not required, being easily purchased (pharmacies, herbalists, internet, etc.), increasing popularity of complementary medicine can be considered as the reasons why people turn to herbal treatments. There are many natural products used in this field and therefore there are different classifications. The classification made by us according to its comprehensiveness and widespread use is given below (Table 4).

Table 3. Weight regain rates for Roux-en-Y gastric bypass (28)

	Weight regain groups			
	<25% N=39	25-30% N=51	30-35% N=73	>35% N=113
Excess weight regain percentage defined as greater than 25% of total weight loss	%38.5	%35.3	%32.9	%38.1
Average weight regain percentage	23.4% N=276			

Table 4. Mechanism of action of phytotherapeutic agents used in the treatment of obesity

A	Those that increase fat burning and stimulate metabolism
B	Appetite suppressants
C	Those that create a feeling of fullness
D	Those who control blood sugar and insulin
E	Those that inhibit the absorption of carbohydrates and fats
F	Those that inhibit inflammation

A. Those that increase fat burning and stimulate metabolism

While they have effects that increase thermogenesis and fat burning, they control energy balance. The most well-known plants that act by stimulating metabolism are sea grape, bitter orange, coffee, green tea and red pepper.

a. Sea grape, Ephedra (*Ephedra sinica*)

Ephedra alkaloids (such as ephedrine) found in the plant are effective on the sympathetic nervous system. Ephedrine reduces appetite by increasing the release of norepinephrine. While its effect on the central nervous system is low, its peripheral effects are much greater than other appetite suppressants. Additionally, ephedrine increases heart rate, blood pressure and thermogenesis (36). The American Food and Drug Administration banned the use of products containing Ephedra in 2004.

b. Fucus, Bladderwrack (*Fucus vesiculosus*)

The most important active ingredient of Fucus vesiculosus, a seaweed, is iodine. Due to their high iodine content, seaweeds increase thyroid hormone production and, accordingly, accelerate metabolism and burn fat. Preparations prepared from the thallus of the plant are marketed as helping to lose weight, but there is no scientific study supporting the effectiveness of the plant in weight loss (37).

c. Bitter orange (*Citrus aurantium*)

Bitter orange (*Citrus aurantium L.*) is a plant whose extract is used to treat many ailments and diseases. Bitter orange extract is also used in weight loss supplements. Because it contains weight loss properties such as appetite control and energy conversion. More than 90% of the protoalkaloids contained in it include p-synephrine, a phenylethylamine derivative structurally similar to ephedrine. Pure p-synephrine increases energy expenditure and accelerates resting metabolism, leading to weight loss. Bitter orange extract not only supports weight loss, but also has antitumor, cytotoxic, sedative, antidiabetic, antioxidant and stomach ulcer protective properties (38).

d. Caffeine and Caffeine-Carrying Plants

Many studies have been conducted on caffeine, thinking that it may cause weight loss due to its thermogenic effect. It is known that caffeine causes thermogenesis by two separate mechanisms (by inhibiting phosphodiesterases responsible for the breakdown of noradrenaline; by stimulating the free fatty acid-triglyceride cycle and the Cori cycle, which converts glycogen and glucose into lactate). Caffeine also suppresses appetite. Although caffeine was found to be a fat burner in studies conducted on experimental animals, no significant change in fat burning was observed with long-term administration to humans, suggesting that the metabolism became insensitive to the effects of caffeine over time (39).

e. Green tea, (*Camellia thea = C. Sinensis*)

In addition to caffeine, green tea contains high amounts of phenolic compounds (epicatechin, epicatechin gallate, epigallocatechin, epigallocatechin gallate [EGCG], fractionin, myrcetin). It is known that catechins have a thermogenic effect by inhibiting the catechol-Omethyl-transferase (COMT) enzyme, which breaks down noradrenaline. Thus, tea has a thermogenic effect both by phosphodiestrease inhibition due to caffeine and by COMT inhibition due to catechins and it is thought that it may be effective in the treatment of obesity. It has also been found that EGCG can prevent the development of adipose tissue by inhibiting angiogenesis, thus it can be used to protect against obesity and prevent WR (38).

f. Guarana (*Paullinia sorbilis = P. cupana*)

It is declared that Guarana seeds are included in the formulation of many recently released products. While a short-term increase in blood pressure and heart rate was observed, the thermogenic effect was observed to be permanent (40).

g. Mexican Pepper (*Capsicum annuum*)

The fruits of the plant contain high amounts of capsaicinoids. These (capsaicin and dihydrocapsaicin) are the active ingredients that give red pepper its burning taste. Capsaicin has been found to increase thermogenesis by dose-dependently increasing catecholamine release from the adrenal medulla. When administered by injection or orally, capsaicin stimulates the sympathetic nervous system, thereby increasing lipid circulation and causing a decrease in adipose tissue mass (39,40).

B. Those Affecting Appetite

Some of the plants in this group regulate intestinal functions due to the fibers they contain. Soluble fibers swell with water and form mass, delaying the absorption of other nutrients, slowing down the increase in postprandial blood sugar and creating a feeling of fullness.

a. Amorphophallus konjac

Three different randomized clinical studies have shown that glucomannan can help lose weight when used 3-4 grams daily. However, the number of subjects used in these studies is very small (n=20-50) and there are some methodologic errors. In another study, glucomannans were found to be ineffective (41).

b. Plantain, Psyllium, Ispaghula (*Plantago ovata*)

The seeds of the plant are widely used in the composition of preparations that help lose weight. Studies have shown that the seeds create a feeling of fullness due to their mucilage content. However, it has been determined that this effect is short-term and although it regulates lipid and glucose metabolism in Type II diabetic patients, it does not have any effect on obesity. The use of seeds in high amounts may cause gastrointestinal side effects such as bloating, nausea, and diarrhea (42). On the other hand, some physicians recommend the use of psyllium to prevent side effects (oily stool, gas, etc.) seen during orlistat treatment (43).

c. Garcinia (*Garcinia cambogia*)

Garcinia fruit and fruit peel extracts are thought to suppress appetite due to the hydroxycitric acid (50%) it carries, increase hepatic glycogen synthesis, and prevent the conversion of carbohydrates to fats and body weight gain through citrate lyase inhibition (37,43). For this reason, this plant is included in most food supplements produced for the treatment of obesity.

d. Gurmar, (*Gymnema sylvestre*)

Gymnemic acid and other triterpenic glycosides found in Gurmar leaves are known to reduce blood glucose levels in diabetic patients. Since excessive carbohydrate intake is among the causes of obesity, plant extracts are also used in the treatment of obesity. The only reported side effect of the extract is decreased taste sensation (40).

e. Hoodia (*Hoodia gordonii*)

It has been found that the substance coded P57, which is obtained from hoodia and has an oxypregnane type triglycoside structure, has an appetite suppressant effect. This substance is one of the substances found in low amounts in the plant extract, but has been isolated as the substance responsible for the appetite suppressant effect of the plant. Although the exact mechanism of action is unknown, it is thought that this compound creates a feeling of fullness by affecting the nervous system (44).

C. Those that create a feeling of fullness

Fiber-Fibrous or Mucilaginous Plants are not broken down or broken down to a small extent during digestion. They are either poorly absorbed or not absorbed. Fibers soften the stool by increasing the weight and volume of the stool. They prevent constipation. They reduce the absorption of sugars from the intestine. They improve blood sugar control and the effects of insulin. They lower blood cholesterol levels and reduce the risk of heart disease. They create a feeling of fullness and do not turn into energy. They should be taken with plenty of water. Daily dietary fiber intake should not exceed 30-40 grams. Flaxseed, maltodextrin, beta glucan fibers, fenugreek fibers can be mentioned.

D. Those Which Control Blood Sugar and Insulin

Medicinal plants with hypoglycemic properties have been used all over the world for many years. There is increasing interest in the use of medicinal plants due to their low price, easy availability, and few or no side effects compared to hypoglycemic drugs. In this field, Moringa oleifera is used as food and traditional medicine to treat diabetes. Various reviews have reported existing evidence for the hypoglycemic property of moringa leaves (45). In general, the majority of studies have shown that consumption of moringa leaves lowers blood sugar. The mechanisms described in these studies for the hypoglycemic effect of moringa leaves include inhibition of α-amylase and α-glucosidase activities, increased glucose uptake in muscles and liver, inhibition of glucose uptake from the intestine, decreased gluconeogenesis in the liver. Additionally, no adverse effects of consumption of moringa leaves were observed in the studies reviewed. However, more human studies are needed (46).

Spices such as cinnamon, clove, bay leaf, and turmeric exhibit insulin-boosting activity in vitro. Among the various types of cinnamon, C. zeylanicum is known as an effective alternative for diabetes. One of the major components in bark oil from Zeylanicum is the 'cinna' aldehyde (roughly 65-80%), which appears to reduce plasma blood glucose concentration more effectively compared to metformin. Cinnamon increases the expression of proteins related to glucose transport and insulin signaling and regulates dyslipidemia (47).

E. Those That Inhibit the Absorption of Carbohydrates and Fats

a. Chitosan

Chitosan is a glucosamine polymer obtained from the shells of animals such as lobsters, crabs and shrimps. It is thought to act by binding to fats and preventing absorption, similar to fibers, but its mechanism of action and effectiveness have not been fully proven. Some researchers think that chitosan may aid weight loss when administered with a calorie-restricted diet. However, according to clinical studies, oral use of chitosan without calorie restriction is not effective in weight loss (48).

b. Carnitine

L-carnitine is an amino acid produced from lysine and methionine in the liver and kidneys. It is necessary for the long-chain fatty acids found in dietary fats to be transported to the mitochondria and converted into energy. In carnitine deficiency, many of the fats taken with food cannot be converted into energy and

accumulate in the body, causing obesity. Many studies conducted in animals have shown that carnitine accelerates the conversion of fats into energy. In a study conducted with volunteers who did and who did not do sports, it was determined that carnitine (4g/day) and antioxidant (vitamin C, vitamin E, methionine) supplementation could increase the exercise performance of those who did sports (49).

F. Inhibitors of Inflammation

Metabolic inflammation is a classic symptom of obesity. Chronic systemic inflammation of obesity can lead to adipose tissue and metabolic changes, and such inflammation is one of the fundamental mechanisms of obesity and metabolic syndrome.

a. Curcumin

Curcumin, also called diferuloylmethane, is the polyphenol of turmeric that is responsible for its yellow color. In addition to being used as a culinary spice, turmeric is also traditionally used as an herbal medicine in Asian countries. It has recently been shown that many of the health advantages of turmeric are attributed to curcumin, as it has anti-tumor, antioxidant, anti-inflammatory, antithrombotic, chemopreventive, antimutagenic, anticancer, anti-atherosclerotic (cardioprotective), lipid-modifying properties, anti-diabetic, antimicrobial, analgesic, pulmonoprotective, antidepressant and anti-aging properties. Curcumin may also provide protective effects regarding exercise-induced oxidative stress and inflammation, muscle soreness, and muscle recovery and performance in physically active individuals (50).

In addition, it has been stated that the consumption of **avenanthramide** extracted from oats, pear extract and malaxinic acid, its main antioxidant component, have antiobesity effects by reducing the inflammatory response by regulating the levels of inflammatory factors and inflammatory pathways (51,52).

CONCLUSION

Studies and publications of natural product extracts with antiobesity properties contain much controversy. High-quality research is needed to definitively determine the safety of the natural products. Some active ingredients and mechanisms of action of natural product extracts have not been identified. Research is needed to elucidate the antiobesity effectiveness and mechanism of action of natural products. There are very few natural products that have entered clinical trials and are approved for the treatment and prevention of obesity, because research data on dosages and active ingredients in animal models raise questions about human bioavailability and the availability of effective treatments. Apart from the mechanisms of action and herbs listed above, many other supplements continue to be used and hopeful in this field. Recently, it has been seen that studies on many effective phytotherapy products have been published in this field. Here, it is necessary to approach herbal products with caution, without knowing the product safety and mechanism of action, that is, those that are not recommended by physicians specialized in the field of phytotherapy.

There is no "Slimming Method" that can be applied to everyone regarding obesity. Weight loss treatment should be started after each individual is evaluated in all aspects and all processes are staged.

Changing lifestyle is the main goal of all treatment methods. Successful weight loss can be achieved through staggering therapy, changing the meals and amounts of food, exercises and increasing calorie expenditure, medical nutrition regulation and the use of phytotherapy products. In case of failure, pharmaceutical drugs and endoscopic methods are applied. If no results are obtained and the patient is morbidly obese, surgical methods should be preferred. Which surgical method should be chosen differs from person to person and should be determined according to accompanying comorbidities.

Studies have shown that no matter which method is chosen, there is a risk of SWL and WR. The risks and side effects of the chosen method should be discussed with the patient. Recommendations to the patient should be given after a multidisciplinary evaluation. Treatment should be started with the most appropriate and least risky method for the patient's current condition. A detailed evaluation should be made to ensure the compliance of the individuals, the deficiencies should be determined and the treatment plan should be made accordingly, and the patient should be assured that there is no patient who will not lose weight through staging. There is no patient who will not lose weight, it just takes time. Providing this assurance will increase patient compliance and success.

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