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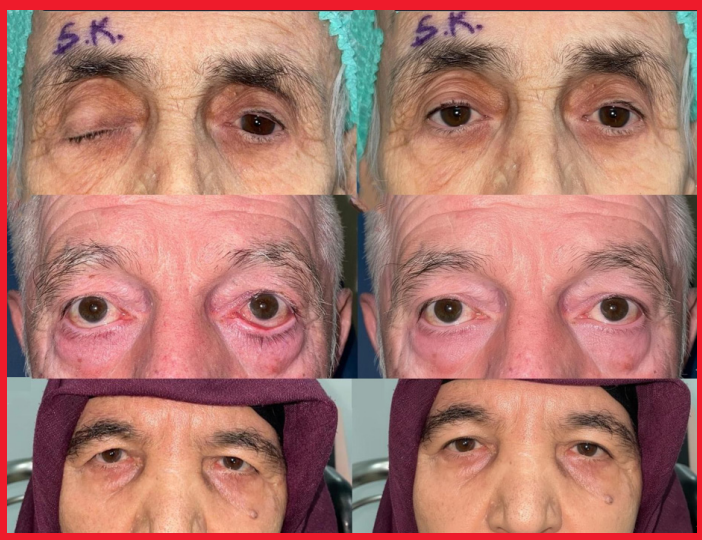

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Phenotype-specific Variations in Vitamin D, Body Mass Index, Insulin Resistance, Anti-Mullerian Hormone, and Lipid Levels in Women with Polycystic Ovary Syndrome

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EDITORIAL

Dear Readers;

We are delighted and proud to present the July 2026 issue of Bezmialem Science journal to our valued readers. In the rapidly evolving and constantly renewing structure of health sciences, sharing scientific knowledge in a reliable, accessible, and applicable manner is more important than ever. For this reason, our journal, which brings together high-quality and innovative research produced in various sub-disciplines of health sciences, continues to build interdisciplinary bridges and contribute to the scientific literature in this issue as well.

The cover image of this issue is selected from the study titled "Clinical Image Correction for Extraocular and Periocular Pathologies and Appearance-related Findings Via an AI-based Image-editing Tool" by Pulat B, Göksu B, Hacıoğlu H, Özkahraman Kırık M, Kırık F, and Özdemir MH. This study evaluates the extent to which the Google Gemini 2.5 Flash Image (Nano Banana) artificial intelligence model can realistically and clinically accurately edit clinical images of periocular and extraocular pathologies using text commands. In analyses performed on clinical photographs representing different eye and periocular pathologies, the AI-generated edits were reviewed by independent experts. The findings show that the model can perform successful image edits while maintaining a high level of realism in many pathologies, and presents a promising approach in the field of clinical image processing.

Other articles featured on the cover include:

"Phenotype-specific Variations in Vitamin D, Body Mass Index, Insulin Resistance, Anti-Mullerian Hormone, and Lipid Levels in Women with Polycystic Ovary Syndrome" by Şanlıkan F et al.

"Comparative Efficacy of Letrozole and Clomiphene in Ovulation Induction for Infertile Females with Comorbidities: A Cross-Sectional Study" by Laraib A et al.

"Measuring the Quality of Life of Patients Undergoing Total or Subtotal Gastrectomy Due to Gastric Cancer" by Güzel M and Akçakaya A.

"Factors Affecting Attachment Loss in Clear Aligner Treatment: A Prospective Clinical Study" by Şahin S et al.

As Bezmialem Vakıf University, with the strength derived from our long-standing foundation tradition, we continue to prioritize ethical principles, academic rigor, and social responsibility in scientific research. We hope that every study published in our journal will not only contribute to the scientific literature but also guide the development of healthcare services, the improvement of patient care, and future research. In this regard, we continue to include original research as well as reviews and case reports that enrich current knowledge, in accordance with scientific quality criteria.

We are also pleased to share an important development for our journal in this issue. Bezmialem Science has achieved a significant milestone in its scientific development journey, rising from category Q4 to category Q3 in the Medicine, General & Internal category according to international academic evaluation criteria. This development is a combined result of our commitment to publishing high-quality scientific studies, our meticulously conducted editorial processes, and the dedicated contributions of our authors and reviewers. In the coming period, we will continue to improve our publication quality and contribute to the national and international scientific community.

I would like to express my sincere thanks to all the authors who contributed their valuable work to the preparation of our July issue, and to our editors and reviewers who conducted the evaluation processes with great dedication and a sense of scientific responsibility. This collaboration and effort, which forms the basis of scientific publishing, will continue to strengthen the academic quality of our journal.

I hope that this third issue of the year will open doors to new ideas and be inspiring for all researchers, academics, and clinicians working in the field of health sciences. I wish you enjoyable reading.

Sincerely,

Prof. Dr. Adem AKÇAKAYA
Editor-in-Chief

Original Article

DOI: 10.14235/bas.galenos.2025.38980
Bezmialem Science 2026;14(3):213-219

Phenotype-specific Variations in Vitamin D, Body Mass Index, Insulin Resistance, Anti-Mullerian Hormone, and Lipid Levels in Women with Polycystic Ovary Syndrome

Polikistik Over Sendromu Fenotipleri Arasında D Vitamini, Vücut Kitle İndeksi, İnsülin Direnci, Anti-Müllerian Hormon ve Lipid Profillerinin Karşılaştırılması

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ABSTRACT

Objective: Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder characterized by diverse phenotypes that differ in metabolic and hormonal risk. The integrated profiles of vitamin D, body mass index (BMI), insulin resistance, anti-Mullerian hormone (AMH), and lipid parameters across these phenotypes remain incompletely defined. The aim of the study was to compare serum 25-hydroxyvitamin D [25(OH)D], AMH, insulin resistance [homeostasis model assessment of insulin resistance (HOMA-IR)], BMI, and lipid profiles among the four PCOS phenotypes defined by the Rotterdam criteria.

Methods: This retrospective study included 420 women aged 18-40 years with PCOS classified as phenotype A (hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology), B (hyperandrogenism and ovulatory dysfunction), C (hyperandrogenism and polycystic ovarian morphology), and D (ovulatory dysfunction and polycystic ovarian morphology). Serum 25(OH)D, AMH, fasting glucose, fasting insulin, and lipid parameters were measured; HOMA-IR was calculated. Data were analyzed using one-way ANOVA or Kruskal-Wallis tests ($p<0.05$ was considered significant).

ÖZ

Amaç: Polikistik over sendromu (PKOS), farklı metabolik ve hormonal risk profillerine sahip çeşitli fenotiplerle karakterize heterojen bir endokrin bozukluktur. Serum 25-hidroksivitamin D [25(OH)D], vücut kitle indeksi (VKİ), insülin direnci [homeostatik model değerlendirmesi-insülin direnci (HOMA-IR)], anti-Müllerian hormon (AMH) ve lipid parametrelerinin bu fenotipler arasındaki bütüncül profilleri halen tam olarak ortaya konulamamıştır. Bu çalışmanın amacı, Rotterdam kriterlerine göre tanımlanan dört PKOS fenotipi arasında serum 25(OH)D, AMH, HOMA-IR, VKİ ve lipid profillerini karşılaştırmaktır.

Yöntemler: Bu retrospektif çalışmaya, 2003 Rotterdam kriterlerine göre PKOS tanısı alan 18-40 yaş arası 420 kadın dahil edildi. Katılımcılar A (hiperandrojenizm, ovulatuvar disfonksiyon ve polikistik over morfolojisi), B (hiperandrojenizm ve ovulatuvar disfonksiyon), C (hiperandrojenizm ve polikistik over morfolojisi) ve D (ovulatuvar disfonksiyon ve polikistik over morfolojisi) fenotipleri olarak sınıflandırıldı. Serum 25(OH)D, AMH, açlık glukozu, açlık insülini ve lipid parametreleri ölçüldü; HOMA-IR hesaplandı. Veriler tek yönlü ANOVA veya Kruskal-Wallis testleri kullanılarak analiz edildi ve $p<0,05$ istatistiksel olarak anlamlı kabul edildi.

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ABSTRACT

Results: Phenotype distribution was A: 35.7%, B: 28.6%, C: 21.4%, and D: 14.3%. Significant inter-phenotype differences were found for BMI, HOMA-IR, AMH, high-density lipoprotein (HDL) cholesterol, and triglycerides (all p<0.01). Phenotypes A and B showed higher mean BMI (31.5±6.1, 30.8±5.8 kg/m²) and HOMA-IR [3.9 (2.8-5.5), 3.7 (2.7-5.1)] and lower HDL cholesterol (41.5±8.5, 42.8±9.1 mg/dL) compared with C and D (p<0.001). Triglycerides were higher in A and B, while AMH was elevated in A [8.8 (6.5-11.2) ng/mL] and C [8.5 (6.8-11.0) ng/mL] versus D [7.1 (5.5-9.5) ng/mL] (p=0.008). No significant differences were observed in vitamin D, total cholesterol, or low-density lipoprotein cholesterol (p>0.05); vitamin D deficiency was prevalent in all phenotypes.

Conclusion: Hyperandrogenic and anovulatory PCOS phenotypes (A and B) exhibit more adverse metabolic profiles with higher BMI, insulin resistance, and dyslipidemia. Vitamin D deficiency was widespread but phenotype-independent. Phenotype-specific evaluation may improve metabolic risk stratification and individualized management in women with PCOS.

Keywords: Polycystic ovary syndrome (PCOS), phenotypes, metabolic risk factors, vitamin D, anti-Mullerian hormone (AMH), insulin resistance

ÖZ

Bulgular: Fenotip dağılımı A: %35,7, B: %28,6, C: %21,4, D: %14,3 idi. Fenotipler arasında VKİ, HOMA-IR, AMH, yüksek yoğunluklu lipoprotein (HDL) kolesterol ve trigliserid düzeylerinde anlamlı fark bulundu (tümü p<0,01). A ve B fenotiplerinde VKİ (31,5±6,1; 30,8±5,8 kg/m²) ve HOMA-IR [3,9 (2,8-5,5); 3,7 (2,7-5,1)] değerleri daha yüksek, HDL kolesterol (41,5±8,5; 42,8±9,1 mg/dL) düzeyi ise C ve D'ye göre daha düşüktü (p<0,001). Trigliserid düzeyleri A ve B'de daha yüksekti. AMH düzeyleri A [8,8 (6,5-11,2) ng/mL] ve C [8,5 (6,8-11,0) ng/mL] fenotiplerinde D fenotipine [7,1 (5,5-9,5) ng/mL] göre anlamlı derecede yüksekti (p=0,008). Serum 25(OH)D, toplam kolesterol ve LDL düzeyleri arasında fark saptanmadı (p>0,05); D vitamini eksikliği tüm fenotiplerde yaygındı.

Sonuç: Hiperandrojenizm ve anovulasyon ile karakterize PKOS fenotipleri (A ve B), daha yüksek VKİ, insülin direnci ve dislipidemi ile seyreden daha olumsuz metabolik profillere sahiptir. D vitamini eksikliği tüm fenotiplerde yaygın olup fenotipten bağımsızdır. Fenotipe özgü değerlendirme, PKOS'lu kadınlarda metabolik risk sınıflandırmasını ve bireyselleştirilmiş yönetimi iyileştirebilir.

Anahtar Kelimeler: Polikistik over sendromu (PKOS), fenotipler, metabolik risk faktörleri, D vitamini, anti-Müllerian hormon (AMH), insülin direnci

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder, and the Rotterdam criteria classify affected women into four phenotypes according to combinations of hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology (PCOM) (phenotypes A-D). This classification is not merely descriptive; it reflects meaningful variability in clinical presentation and longer-term metabolic risk and therefore offers a practical framework for risk stratification and individualized care (1-3).

From a pathophysiologic perspective, body mass index (BMI), insulin resistance [commonly estimated by the homeostasis model assessment, homeostasis model assessment of insulin resistance (HOMA-IR)], anti-Mullerian hormone (AMH), vitamin D status, and lipid parameters represent interrelated domains that help explain both the reproductive and cardiometabolic expression of PCOS. Prior studies show that vitamin D deficiency is frequent in PCOS and associates with adverse metabolic features; AMH—although a marker of follicular dynamics—also varies across phenotypes and may align with disease severity; insulin resistance and adiposity are central to metabolic risk; and dyslipidemia [lower high-density lipoprotein (HDL) cholesterol and higher triglycerides] characterizes the atherogenic profile often seen in PCOS. These markers were selected a priori because, together, they capture hormonal milieu (AMH), nutritional/endocrine modulation (vitamin D), core metabolic load (BMI and HOMA-IR), and downstream cardiovascular risk (lipids)—domains that map onto phenotype-level differences and are relevant to routine clinical decision-making (4-7).

Despite this rationale, the combined, phenotype-specific profile of these parameters was incompletely defined. Our study addresses this gap by comparing serum 25-hydroxyvitamin D [25(OH)D], AMH, insulin resistance (HOMA-IR), BMI, and a standard lipid panel across the four Rotterdam phenotypes in a well-characterized cohort, minimizing redundancy by listing the parameters once here and applying them consistently in the analyses that follow (8,9).

This phenotype-anchored approach has direct clinical implications. If hyperandrogenic phenotypes (A and B) demonstrate higher BMI, greater insulin resistance, and a more atherogenic lipid profile than phenotypes C and D—as our data indicate—then clinicians can prioritize early metabolic screening (oral glucose tolerance or HOMA-IR estimation), aggressive weight-centered interventions, lipid management, and cardiometabolic counseling in these groups. Conversely, in phenotypes where AMH is relatively higher without commensurate metabolic burden, emphasis may be placed on reproductive planning and ovulation-focused strategies. Similar vitamin D levels across phenotypes suggest that deficiency screening and replacement should be considered broadly in PCOS rather than restricted to a single phenotype. In sum, classifying patients by Rotterdam phenotype can guide practical, phenotype-sensitive choices in diagnostic work-up (e. g., frequency and intensity of metabolic testing) and in management (e. g., lifestyle targets, pharmacotherapy for

insulin resistance or dyslipidemia), thereby operationalizing precision care in everyday practice (10-12).

Methods

This retrospective cross-sectional study was conducted using data of patients diagnosed with PCOS between January 1, 2020 and January 1, 2025 at University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital, Department of Gynecology and Obstetrics. Ethical approval was obtained (University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital, 05 June 2025, decision no: 2025/010.99/17/41), and all data were anonymized. Due to the retrospective design of the study and the use of anonymized data, the requirement for informed consent was waived by the institutional ethics committee.

A total of 420 women aged 18-40 years with a definite diagnosis of PCOS according to the 2003 Rotterdam criteria (at least two of the following: oligo/anovulation, clinical or biochemical hyperandrogenism, PCOM on ultrasound) and complete laboratory data (vitamin D, AMH, insulin resistance parameters, and lipid profile) were included.

Phenotype Assignment and Diagnostic Definitions

Patients were categorized into four phenotypes based on the combination of diagnostic features: A=hyperandrogenism + ovulatory dysfunction + polycystic ovaries; B=hyperandrogenism + ovulatory dysfunction; C=hyperandrogenism + polycystic ovaries; D=ovulatory dysfunction + polycystic ovaries.

Clinical hyperandrogenism was defined using the modified Ferriman-Gallwey (mFG) score, which assesses terminal hair growth in nine body areas (upper lip, chin, chest, upper and lower back, upper and lower abdomen, upper arm, thigh). Each site was scored from 0 (no terminal hair) to 4 (extensive growth), and scores were summed to yield a total between 0 and 36. An mFG score ≥8 was accepted as indicative of clinical hyperandrogenism. Biochemical hyperandrogenism was defined when at least one androgen parameter (total testosterone, free androgen index, or dehydroepiandrosterone sulfate) exceeded laboratory reference ranges.

Waist circumference was measured in centimeters with a flexible non-elastic tape at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest, while the participant was standing and at the end of gentle expiration. BMI was calculated as weight (kg) divided by height squared (m^2). Ovulatory dysfunction was defined as oligomenorrhea (cycle length >35 days or <8 cycles per year) or amenorrhea (≥90 days without menses). Menstrual cycle length was recorded as the average number of days between spontaneous bleeding episodes in the preceding 12 months. PCOM was defined as ≥12 follicles measuring 2-9 mm in diameter in at least one ovary and/or an ovarian volume >10 cm^3 on transvaginal ultrasound.

Exclusion Criteria

Women with endocrinopathies mimicking PCOS (non-classical congenital adrenal hyperplasia, Cushing syndrome, hyperprolactinemia, thyroid dysfunction, androgen-secreting tumors), serious systemic diseases (chronic hepatic/renal failure, cardiovascular disease, uncontrolled diabetes, active malignancy, autoimmune disorders), pregnancy, use of relevant medications (hormones, steroids, high-dose vitamin D in the previous 3 months), or missing data were excluded.

Laboratory Assessments

Morning fasting venous blood samples were analyzed in the central laboratory using standardized and quality-controlled methods.

- 25(OH)D: Automated chemiluminescent immunoassay (ng/mL).
- AMH: Automated enzyme immunoassay (ng/mL).
- Fasting glucose: Hexokinase method; fasting insulin: automated immunoassay; HOMA-IR=[fasting insulin (μIU/mL)×fasting glucose (mg/dL)]/405.
- Lipid profile: Total cholesterol, HDL, low-density lipoprotein (LDL), and triglycerides via enzymatic colorimetric assays (mg/dL).

Statistical Analysis

Analyses were performed using SPSS. Normality was assessed with the Shapiro-Wilk test and histograms. Continuous variables were compared among phenotypes using one-way analysis of variance (post-hoc Tukey/Bonferroni) or Kruskal-Wallis (post-hoc Dunn's) tests as appropriate. A p-value <0.05 was considered statistically significant. Post-hoc pairwise comparisons were explicitly performed to determine which phenotypes differed from each other. In all tables, statistically significant between-group differences are indicated by superscript letters or footnotes (e. g., A>C&D, $p<0.05$).

Rationale for the Absence of a Control Group

Because the study aimed to examine intra-PCOS phenotype differences, not PCOS versus healthy controls, no control group was included. Healthy population metabolic data are well-established in the literature, and our focus was to delineate phenotype-specific risk variation among PCOS patients.

Results

The basic demographic and clinical characteristics of the 420 PCOS patients included in the study, according to phenotypes, are presented comparatively in Table 1. Phenotype A constituted 35.7% of the study population, phenotype B 28.6%, phenotype C 21.4%, and phenotype D 14.3%. While no statistically significant difference was

observed between the groups in mean age (p=0.152), statistically significant differences were observed between the phenotypes in terms of BMI, waist circumference, mFG score, and mean menstrual cycle length (p<0.001). Specifically, BMI and waist circumference were statistically significantly higher in hyperandrogenic and anovulatory phenotypes A and B compared to the other phenotypes. Similarly, the mFG score was statistically significantly higher in phenotypes A, B, and C, which included hyperandrogenism, as expected, compared to phenotype D. Median menstrual cycle length values were statistically significantly longer in phenotypes A, B, and D, which included anovulation, than in phenotype C, which had regular menstruation. Comparison of baseline hormonal and metabolic parameters examined in our study among PCOS phenotypes revealed statistically significant differences (Table 2). Median values of BMI, which is critical for metabolic risk, and HOMA-IR, which reflects insulin resistance, were observed to be statistically significantly higher in the hyperandrogenic phenotypes phenotype A and phenotype B compared to the normoandrogenic phenotype D and the ovulatory phenotype C (p<0.001). A similar trend was observed in the lipid profile; median triglyceride values were statistically significantly higher in phenotypes A and B (p<0.001), and mean HDL cholesterol, known to be protective, was statistically significantly lower in these two groups compared to phenotypes C and D (p<0.001).

AMH levels, which are associated with ovarian reserve, also demonstrated statistically significant differences between phenotypes (p=0.008); specifically, phenotypes A and C had higher median values than phenotype D. However, serum 25(OH)D levels, which were generally low across the entire patient group, were not statistically significantly different among the four phenotype groups (p=0.315). Similarly, mean total cholesterol and LDL cholesterol levels did not differ statistically significantly between phenotypes (p=0.188 and p=0.240, respectively).

Discussion

The present study provides a detailed phenotype-based assessment of metabolic and hormonal characteristics among women with PCOS. Our findings confirm that the hyperandrogenic phenotypes (A and B) exhibit a more adverse metabolic profile, with statistically significantly higher BMI, waist circumference, insulin resistance (HOMA-IR), and triglyceride levels, as well as lower HDL cholesterol, compared to the ovulatory or normoandrogenic phenotypes (C and D). These results are consistent with several

Table 1. Baseline demographic and clinical characteristics of patients according to phenotypes

Feature	Phenotype A (n=150)	Phenotype B (n=120)	Phenotype C (n=90)	Phenotype D (n=60)	p-value
Age (years, mean ± SD)	28.1±4.9	28.8±5.3	28.5±5.0	28.0±5.5	0.152
BMI (kg/m², mean ± SD)	31.5±6.1^{ab}	30.8±5.8^{ab}	28.1±5.2^{c}	27.5±4.9^{c}	<0.001
Waist circumference (cm, mean ± SD)	96.5±11.2^{ab}	94.8±10.5^{ab}	89.1±9.8^{c}	87.5±9.1^{c}	<0.001
mFG score [median (IQR)]	11 (8-15)^{a}	10 (7-14)^{a}	9 (6-13)^{a}	4 (2-6)^{b}	<0.001
Cycle length [days, med (IQR)]	55 (40-90)^{a}	60 (45-95)^{a}	29 (27-31)^{b}	50 (38-85)^{a}	<0.001

P-value calculated by ANOVA, Kruskal-Wallis or chi-square test. There is a statistically significant difference in post-hoc tests between groups with different superscript letters (^{a,b,c}) in the same row (p<0.05)
ANOVA: Analysis of variance, BMI: Body mass index, mFG: Modified Ferriman-Gallwey, SD: Standard deviation, IQR: Interquartile range

Table 2. Comparison of clinical and laboratory parameters according to PCOS phenotypes

Parameter	Phenotype A (n=150)	Phenotype B (n=120)	Phenotype C (n=90)	Phenotype D (n=60)	p-value
BMI (kg/m², mean ± SD)	31.5±6.1^{ab}	30.8±5.8^{ab}	28.1±5.2^{c}	27.5±4.9^{c}	<0.001
25(OH)D (ng/mL, mean ± SD)	16.2±7.5	17.1±8.0	17.5±8.8	18.0±9.1	0.315
AMH [ng/mL, median (IQR)]	8.8 (6.5-11.2)^{a}	8.2 (6.1-10.8)^{ab}	8.5 (6.8-11.0)^{a}	7.1 (5.5-9.5)^{b}	0.008
HOMA-IR [median (IQR)]	3.9 (2.8-5.5)^{ab}	3.7 (2.7-5.1)^{ab}	2.9 (2.0-4.0)^{c}	2.6 (1.9-3.8)^{c}	<0.001
Total cholesterol (mg/dL, mean ± SD)	195±35	192±38	188±33	185±30	0.188
HDL cholesterol (mg/dL, mean ± SD)	41.5±8.5^{ab}	42.8±9.1^{ab}	46.5±9.8^{c}	47.8±10.2^{c}	<0.001
LDL cholesterol (mg/dL, mean ± SD)	115±30	112±32	110±28	108±25	0.240
Triglycerides [mg/dL, median (IQR)]	155 (110-210)^{ab}	148 (105-195)^{ab}	125 (90-160)^{c}	118 (85-155)^{c}	<0.001

P-value was calculated by ANOVA or Kruskal-Wallis tests. There is a statistically significant difference in post-hoc tests between groups with different superscript letters (^{a,b,c}) in the same row (p<0.05)
ANOVA: Analysis of variance, SD: Standard deviation, IQR: Interquartile range, PCOS: Polycystic ovary syndrome, BMI: Body mass index, 25(OH)D: Serum 25-hydroxyvitamin D, AMH: Anti-Mullerian hormone, HOMA-IR: Homeostasis model assessment of insulin resistance, HDL: High-density lipoprotein, LDL: Low-density lipoprotein

previous reports emphasizing that hyperandrogenism and anovulation jointly contribute to worsened cardiometabolic risk in PCOS (3,8,9).

When analyzed individually, phenotype A (hyperandrogenic + anovulatory + PCOM) demonstrated the most pronounced metabolic deterioration, aligning with Yilmaz et al. (8) and Panidis et al. (9), who reported that phenotype A carried the highest insulin resistance and dyslipidemia burden. Phenotype B, which also includes hyperandrogenism and anovulation but lacks PCOM, demonstrated a similar but slightly less severe metabolic profile, suggesting that ovulatory dysfunction and androgen excess rather than ovarian morphology primarily drive metabolic abnormalities. Phenotype C (hyperandrogenic + PCOM with regular cycles) maintained higher AMH levels and mFG scores than phenotype D but exhibited more favorable metabolic indices, reflecting the potential mitigating effect of preserved ovulatory function. Finally, phenotype D, characterized by ovulatory dysfunction and PCOM but without hyperandrogenism, represented the mildest metabolic profile, corroborating prior evidence that normoandrogenic phenotypes have lower cardiovascular and metabolic risk (9,13,14).

Waist circumference and BMI, both markers of central and total adiposity, were statistically significantly elevated in phenotypes A and B. Central adiposity plays a crucial role in insulin resistance and androgen excess, and our data support the strong correlation between abdominal fat accumulation and metabolic risk in PCOS (13,15).

Similarly, the mFG score, which quantifies the degree of hirsutism, was statistically significantly higher in phenotypes A, B, and C—all of which include hyperandrogenism—consistent with the pathophysiologic link between androgen excess and clinical hair growth (3,9). Menstrual cycle length was also markedly prolonged in anovulatory phenotypes A, B, and D, aligning with the expectation that ovulatory dysfunction manifests clinically as oligomenorrhea or amenorrhea. These findings collectively reinforce that both reproductive and metabolic features vary systematically across Rotterdam phenotypes.

AMH levels differed significantly among PCOS phenotypes in the present study, with higher concentrations observed in phenotypes A and C compared with the normoandrogenic phenotype D. This finding is consistent with previous reports demonstrating that AMH is closely related to follicle number, granulosa cell activity, and androgen excess rather than directly reflecting metabolic severity (10,11). Importantly, although phenotypes A and C exhibited higher AMH levels, our study design does not allow conclusions regarding a causal relationship between AMH and metabolic disturbances. The observed differences in AMH should therefore be interpreted as phenotype-associated hormonal variations rather than indicators of metabolic burden.

In this context, AMH may be considered a complementary biomarker reflecting ovarian and endocrine characteristics across PCOS phenotypes, rather than a direct marker of insulin resistance or cardiometabolic risk. The coexistence of elevated AMH and adverse metabolic features in phenotype A likely reflects the clustering of hyperandrogenism, anovulation, and ovarian dysfunction within this phenotype, rather than a direct pathophysiological role of AMH in metabolic dysregulation. Future prospective studies incorporating longitudinal follow-up and multivariable analyses are needed to clarify whether AMH has any independent predictive value for metabolic outcomes in women with PCOS.

Despite the widespread vitamin D deficiency observed across all groups, we observed no statistically significant inter-phenotype difference. This aligns with the findings of Eftekhar et al. (7) and He et al. (16), though some studies suggested lower vitamin D levels in hyperandrogenic phenotypes (7,12). Given that vitamin D deficiency is nearly widespread in PCOS, factors such as sun exposure, dietary intake, and genetic variation likely override phenotype-based differences (16,17). Nevertheless, consistent deficiency underscores the need for population-wide vitamin D screening in women with PCOS, regardless of phenotype.

The novelty of this study lies in its comprehensive evaluation of both hormonal and metabolic parameters across all four Rotterdam phenotypes within a large, single-center cohort, integrating anthropometric, biochemical, and endocrine indices into a unified comparison. By highlighting that each phenotype exhibits a distinct combination of metabolic, reproductive, and biochemical characteristics, this work strengthens the rationale for phenotype-specific risk stratification in clinical practice. From a practical standpoint, phenotypes A and B should be monitored more closely for metabolic syndrome, dyslipidemia, and insulin resistance, whereas phenotype C may primarily benefit from reproductive-focused management. Phenotype D patients, though metabolically milder, may still require long-term follow-up for reproductive dysfunction. These phenotype-based distinctions can guide individualized counseling, diagnostic testing, and early intervention strategies, aligning with precision medicine principles in PCOS management (13,14,18).

Study Limitations

This study has several limitations that should be acknowledged. First, its retrospective and single-center design precludes causal inferences between PCOS phenotypes and metabolic or hormonal parameters; therefore, the observed associations should be interpreted descriptively rather than as cause-effect relationships. Second, because data were collected from medical records, variability in clinical and laboratory measurements could not be entirely excluded. In particular, serum 25(OH)D

levels were measured at different times of the year, and information on seasonal variation, sun exposure, dietary intake, and supplementation was not available, which may have attenuated potential phenotype-related differences. Third, insulin resistance was assessed using HOMA-IR, a widely accepted but indirect surrogate marker; more advanced methods such as euglycemic-hyperinsulinemic clamp studies were not feasible in this retrospective setting. Additionally, lifestyle-related factors including physical activity, dietary habits, smoking, and alcohol consumption were not systematically recorded and therefore could not be included in the analyses. The absence of a healthy control group limits comparisons with the general population; however, the primary aim of this study was to evaluate intra-PCOS phenotype differences rather than PCOS versus non-PCOS comparisons. Despite these limitations, the major strength of the study lies in its relatively large sample size and comprehensive, phenotype-based evaluation of anthropometric, metabolic, and hormonal parameters within a well-defined PCOS cohort.

Conclusion

By expanding the comparative analysis beyond metabolic indices to include anthropometric and clinical features such as waist circumference, mFG score, and menstrual cycle length, our study provides a nuanced understanding of how distinct PCOS phenotypes manifest across multiple biological dimensions. The differential pattern of AMH further emphasizes the endocrine diversity of the syndrome. Collectively, these findings add novel evidence supporting integrated, phenotype-based evaluation as a cornerstone for improving diagnostic accuracy and optimizing personalized management in PCOS, particularly in guiding phenotype-oriented metabolic screening strategies in routine clinical practice.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital, on 05 June 2025 (decision no: 2025/010.99/17/41).

Informed Consent: Waived by the ethics committee.

Footnotes

Authorship Contributions

Surgical and Medical Practices: F.Ş., İ.B., E.M., M.A., Concept: F.Ş., E.K., U.K.Ö., M.A., Design: F.Ş., İ.B., E.K., E.M., Data Collection or Processing: F.Ş., İ.B., M.A., Analysis or Interpretation: F.Ş., İ.B., E.K., U.K.Ö., E.M., Literature Search: F.Ş., İ.B., U.K.Ö., E.M., M.A., Writing: F.Ş., İ.B., E.K., M.A.

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Original Article

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β-sitosterol, A Potential Enzyme Inhibitor Molecule From *Nepeta* Species: *In vitro* and *In silico* Approaches

Nepeta Türlerinden Elde Edilen Potansiyel Bir Enzim Inhibitörü Molekülü β-sitosterol: *In vitro* ve *In silico* Yaklaşımlar

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ABSTRACT

Objective: In the literature, β-sitosterol (BS), one of the primary phytosterol components found in plant-based dietary sources, has been reported to exhibit antidiabetic, antimicrobial, enzyme-inhibiting, anti-inflammatory, antioxidant, trypanocidal, anticancer, and antinociceptive effects. Therefore, in our present study, we aimed to isolate BS from the genus *Nepeta* (*N. trachonitica*, *N. aristata*, *N. italica*, *N. baytopii*, and *N. stenantha*) using column chromatography (silica gel) and to elucidate BS using chromatographic methods (NMR and MS).

Methods: Detailed studies (*in vitro* and *in silico*) were conducted on metabolic enzymes (carbonic anhydrase, tyrosinase, α-amylase, urease, α-glucosidase, and lipase) of BS, isolated as the main component from five different *Nepeta* species, and statistically compared with standard drugs.

Results: It was observed that BS had effective inhibitory effects when compared with standard drugs in inhibiting urease (IC_{50}, 21.60±0.01 μM) and tyrosinase (IC_{50}, 6.60±0.02 μM). In kinetic studies, BS was found to have an effective inhibitory capacity on α-glucosidase with an inhibitory constant of 25.67 μM. BS was found to have a high binding affinity with tyrosinase in molecular docking. In addition, the complex of tyrosinase and BS, which had not undergone molecular dynamics simulation

ÖZ

Amaç: Literatürde, bitki bazlı besin kaynaklarının temel fitosterol bileşenlerinden biri olan β-sitosterolün (BS), antidiyabetik, antimikrobiyal, enzim inhibitörü, antienflamatuvar, antioksidan, tripanosidal, antikanser ve antinosiseptif etkilere sahip olduğu bildirilmiştir. Bu nedenle, mevcut çalışmamızda BS, *Nepeta* cinsinden (*N. trachonitica, N. aristata, N. italica, N. baytopii* ve *N. stenantha*) kolon kromatografisi (silika jel) kullanılarak izole edilmesi ve BS'nin kromatografik yöntemler (NMR ve MS) kullanılarak aydınlatılması amaçlanmıştır.

Yöntemler: Beş farklı *Nepeta* türünden ana bileşen olarak izole edilen BS'nin metabolik enzimleri (karbonik anhidraz, tirozinaz, α-amilaz, üreaz, α-glukozidaz, lipaz) üzerinde detaylı çalışmalar (*in vitro* ve *in silico*) yürütülmüş, standart ilaçlarla istatistiksel olarak karşılaştırılmıştır.

Bulgular: BS standart ilaçlarla karşılaştırıldığında üreazı (IC_{50}, 21,60±0,01 μM) ve tirozinazı (IC_{50}, 6,60±0,02 μM) inhibe etmede güçlü inhibitör etkilere sahip olduğu gözlenmiştir. Kinetik çalışmalarda, BS'nin 25,67 μM'lik bir inhibitör sabiti ile α-glukozidaz üzerinde etkili bir inhibitör kapasitesine sahip olduğu bulunmuştur. BS'nin moleküler yerleştirmede tirozinaz ile yüksek bağlanma afinitesine sahip olduğu bulunmuştur. Ayrıca, daha önceki çalışmalarda moleküler dinamik

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ABSTRACT

in previous studies, reached stability at 4 nm in the RMSD graph, and the binding energy was recorded as -4.39 kcal/mol in the MM/PBSA analysis.

Conclusion: The *in silico* results supported that *Nepeta* species and BS are effective on the dermatological enzyme (tyrosinase) and may be candidates for a new dermatological product.

Keywords: *Nepeta* species, β-sitosterol, *in vitro* activities, *in silico* studies

ÖZ

simülasyonu yapılmayan tirozinaz ve BS kompleksi, RMSD grafiğinde 4 nm'de kararlılığa ulaşmış ve bağlanma enerjisi MM/PBSA analizinde -4,39 kcal/mol olarak kaydedilmiştir.

Sonuç: *In silico* sonuçlar, *Nepeta* türlerinin ve BS'nin dermatolojik enzim (tirozinaz) üzerinde etkili olduğunu ve yeni bir dermatolojik ürün adayı olabileceğini desteklemektedir.

Anahtar Kelimeler: *Nepeta* türleri, β-sitosterol, *in vitro* aktiviteler, *in silico* çalışmalar

Introduction

Plants produce phytochemicals to facilitate environmental adaptation, resist stress conditions, ensure survival, and provide chemical defense against insects and harmful microorganisms. Phytochemicals can be divided into phenols, alkaloids, and terpenes (1). These compounds exhibit diverse biological properties, including antioxidant activity, antimicrobial effects, enzyme inhibition, and immune system stimulation (2). The Lamiaceae family is represented in the flora of Türkiye by 45 genera, 565 species, and 735 taxa. *Nepeta*, one of the most abundant genera of the Lamiaceae family, includes 34 species and 40 taxa in Türkiye (3). *Nepeta* species have rich content in terms of nepetalactone, diterpene, triterpene, sesquiterpene, and iridoids (4).

Triterpenes, a group of natural compounds, are transformed into metabolites such as saponins, steroids, and sterols in the cell (5). Phytosterols are a subgroup of steroids, a class of important bioorganic molecules widely distributed in fungi, plants, and animals (6). It is structurally similar to cholesterol. The European Food Safety Authority recommends consuming approximately 1.5-2.4 g of phytosterols per day to lower blood cholesterol levels. At the same time, the Food and Drug Administration states that the role of sterol/phytosterol is at least 1.3 g/day in reducing the risk of heart disease (6). Stigmasterol, campesterol, and β-sitosterol (BS) are the dominant phytosterols in human herbal nutrition. BS has antidiabetic, antimicrobial, enzyme-inhibiting, anti-inflammatory, antioxidant, anticancer, trypanocidal, and antinociceptive effects (7). It is also used as an antidote against snake venom (6).

The Norwegian Food Safety Authority says BS can be used in sunscreens, moisturizers, body washes, and anti-aging cosmetics due to its skin-regulating effect (8). In one study, BS was reported to block the production and messenger RNA expression of thymic stromal lymphopoietin by inhibiting the caspase-1 and nuclear factor-kB signaling pathways in the stimulated human mast cell line HMC-1 cells (9). It is known that various plant species containing phytosterols have been used for centuries to treat wounds and skin burns (8). In a study conducted in mice, BS reduced clinical symptoms such as eczema, dryness, and erythema, serum histamine, and immunoglobulin E levels in 2,4-dinitrochlorobenzene-induced atopic dermatitis and histamine-induced itching. BS was found to inhibit the expression of interleukin-6 in atopic dermatitis-like skin lesions and HaCaT cells (10).

Biological macromolecules, which are considered the main components of drugs used in treating diseases, contribute to the treatment by inhibiting enzymes. Recently, enzyme inhibitors accounted for almost half of the drugs used for clinical purposes. Research on the human genome reveals that enzymes predominate in the disease-relevant regions that code for the targets to which drugs are directed. Future pharmacological research is expected to continue to concentrate on precise enzyme inhibition. For this reason, enzymes have recently become the target of major pharmaceutical and biotechnology companies' efforts in discovering and developing new drugs (11). *In silico* studies are conducted to support experimental investigations of the interaction between enzymes and molecules in a computer environment. This provides time and economic advantages.

For this purpose, the enzyme inhibitory activities (urease, carbonic anhydrase (CA), tyrosinase, lipase, α-amylase, and α-glucosidase) of BS isolated from the *Nepeta* genus (*N. trachonitica, N. aristata, N. italica, N. baytopii,* and *N. stenantha*) were determined. Enzyme kinetics, molecular dynamics (MD), molecular docking, and molecular mechanics Poisson-Boltzmann surface area (MM/PBSA) analysis were investigated. In this study, inhibition of urease, CA, lipase, and tyrosinase, and inhibition kinetics of these enzymes and the complex of tyrosinase enzyme and BS, which did not have an MD simulation, and MM/PBSA analysis in previous studies, were investigated for the first time. The study aims to provide new perspectives on the existing literature by conducting further research on BS, which is known to have high activity.

Methods

Collection of Plant Material and Extraction of the *Nepeta* Genus

N. aristata Boiss. & Kotschy (BIN6195, Endemic), *N. baytopii* Hedge & Lamond (BIN5933, Endemic), *N. italica* L. (BIN7496), *N. stenantha* Kotschy & Boiss., and *N. trachonitica* Post (BIN7722) were collected and identified by Prof. Dr. Lütfi Behçet. The plants were deposited in the herbarium of Bingöl University, Türkiye.

The aerial parts of five *Nepeta* species were ground, dried, and extracted using a chloroform: methanol (1:1) mixture. This extraction was repeated three times. The extracts were filtered through filter paper (Whatman No. 1). The solvent in the extract was removed using a rotary evaporator. The extracts were then dried and stored for use in activities after being lyophilized. The crude extracts were fractionated by column chromatography using a silica gel column with increasing solvent polarity. Various subfractions were obtained in silica gel 60 and Sephadex LH-20 columns. Similar fractions were analyzed using the TLC profile, merged to save time and consumables, and the number of fractions decreased.

Fraction and Isolation

Extracts were separated on the column (silica gel) by changing the solvent from low polarity to high polarity. Various subfractions of the fractions were obtained using silica gel and the Sephadex column. Similar fractions were analyzed using TLC profiling, merged to save time and consumables, and the number of fractions was decreased. BS was isolated using column chromatography (silica gel) as follows; *N. baytopii* from the first fraction of the chloroform extract, *N. italica* from the first fraction of the chloroform extract using Sephadex LH20 column chromatography; *N. aristata* from the fifth fraction of the chloroform extract, *N. stenantha* from the third fraction of the chloroform extract, and *N. trachonitica* from the sixth fraction of the chloroform extract.

Nuclear Magnetic Resonance (NMR) Spectroscopy Analysis

The NMR spectrometer was used to get the ^{13}C (Agilent at 150 MHz) and ^{1}H (Agilent at 600 MHz) NMR spectra of samples in CD_3OD to determine the molecule's structure. Additionally, three different 2D NMR spectra were utilized with COSY, HSQC, and HMBC (11,12).

Mass Spectrometry (MS)

An MS integrated with an Agilent 6460 Triple Quad brand liquid chromatography (HPLC) system was used to confirm the BS's mass, whose structure was determined. After the analytical column was taken out, the eluent (acetonitrile + ammonium formate and formic acid) was added. It was performed with a 4 µL injection volume and a 0.400 mL/min solvent flow. The application was completed in a total of 120 seconds in the 50-1200 m/z scanning range. MS spectra were generated as a result of the specified adjustments (13).

Enzyme Kinetics and Inhibitions

Inhibitions of BS with urease (14), CA (15), tyrosinase (16), α-amylase (17), α-glucosidase (18), and lipase (19) enzymes, as well as inhibition categories and binding constants, were determined spectrophotometrically using the BIOTEK (Epoch 2) microplate reader. The inhibition findings were used to calculate half-maximal drug inhibitory concentration (IC_{50}) values (µg/mL) of all inhibition results. Michaelis-Menten and Lineweaver-Burk graphs were made with varying quantities and substrates to ascertain the enzyme's kinetics. BS's inhibitor constant (K_i) was calculated using the V_{max} and K_m values from the Lineweaver-Burk chart (11).

Molecular Interaction Applications

Chem Draw Ultra 18.0 was used to draw the BS structure, and Chem3D 18.0 was used to compute the lowest energy. The enzymes used in our tests, which were selected from the protein database (RCSB PDB: Homepage), utilized 3D protein structures. α-amylase from porcine pancreas (1OSE), urease from Jack bean (4GY7), lipase from porcine pancreas (1HPL), α-glucosidase from *Saccharomyces cerevisiae* (3AJ7), CA from Bovine erythrocytes (3HS4), tyrosinase from mushroom (5M6B) were selected. To determine the interaction of the molecule with the active site of the enzymes. 2D and 3D images and data of the structure formed by the compound and the enzyme were taken using the Discovery Studio program. Based on the binding affinities, the binding constants (K_i) and the binding affinities were calculated in Excel (3,20).

MD Simulations and MM/PBSA Analysis

The MD simulation used BS's interactions with highly active enzymes within 100 ns to examine its dynamic mobility. GROMACS software was utilized for this simulation. Conducted utilizing the TIP3P water dissolving method in conjunction with the force field (Charmm36-July-2022) at 310 K. To neutralize the system and equalize the charge, ions (Na^+ and Cl^-) were added. Ligand topology was generated via the CGenFF server. After the NVT step, the temperature is increased to 310 K by integrating the temperature using a 100-ps V scale. The system was further stabilized by positional restraint of the backbone atoms using the Parrinello-Rahman barostat with NPT and a coupling constant of 0.1 ps. After the adjustments were completed, the MD simulation was run for 100 ns. Along the way, the integrated GROMACS software tools were used to examine the hydrogen bonding, root-mean-square fluctuation (RMSF), radius of gyration (Rg), and root mean square deviation (RMSD). The charts were generated using GRACE software. The MM/PBSA method was used to calculate the complex's binding free energy.The "gmx_

mmpbsa" tool was used to determine the binding free energies for each complex (20,21).

Statistical Analysis

The findings of *in vitro* tests were used to calculate biological activity ± standard deviations. For statistical parameters, the IBM SPSS 20.0 software was utilized, and an analysis of variance test was used. Based on the multiple comparison analysis results, the Tukey HSD[a,b] test was used. Statistical significance was expressed as $p<0.05$.

Results

In the silica gel column, plant extracts were divided into fractions based on increasing solvent polarity (*n*-hexane, chloroform, ethyl acetate, and methanol). The resulting fractions were divided into subfractions in a silica gel 60 and a Sephadex LH-20 column. Accordingly, the BS molecule was isolated from *N. aristata* (Fr5 in Sephadex column), *N. stenantha* (Fr3 in Sephadex column), *N. trachonitica* (Fr6 in sephadex column), *N. baytopii* (Fr1 in the silica-gel column), and *N. italica* (Fr1 in the silica-gel column) (Figure 1).

Structural Analysis of BS by NMR Techniques

In the structure determination of BS, as a result of ^{1}H-NMR analysis, complex signals in the aliphatic region revealed that the molecule was a phytosterol. Accordingly, the specific olefinic signal at 5.34 ppm indicated the presence of a double bond in the structure. The signals in the 0.6-1.2 ppm range indicated the presence of methyl groups, and the signal at 3.51 ppm confirmed that the oxygen atom was bonded. When the COSY interactions of the signals at 2.25-2.28 ppm were examined, it was observed that these signals indicated the -CH2 group was adjacent to an electronegative region. Examination of HSQC and HMBC interactions, as well as a comparison of ^{1}H- and ^{13}C-NMR data from the literature, confirmed that the structure is BS (Figure 2 and Table 1) (22). The molecule has the chemical formula $C_{29}H_{50}O$. Its (m/z) mass was calculated to be 414.71 negative ion/mass and confirmed with literature information.

Enzyme Inhibitions and Kinetic Assays

All living cells use enzymes to catalyze reactions in various biological functions. Because modifying enzyme function yields precise and rapid consequences, enzymes remain the primary targets for drug development. Even while the number of medications used to alter extracellular signaling receptors is growing, 47% of the medications on the market now block enzyme targets (23).

Studies were conducted on BS's urease, CA, tyrosinase, lipase, α-amylase, and α-glucosidase enzymes. Lineweaver-Burk plots of the inhibition kinetics of BS with enzymes are shown in Figure 3. Compared with the standards used in enzymes, it was determined that BS showed high efficacy in urease and tyrosinase inhibition (Table 2).

Molecular Docking

Five alkyl contacts with ARG439, ALA440, MET588, and MET637, as well as four pi-alkyl (P-A) interactions with HIS492 and HIS519, were found for BS, which interacts with

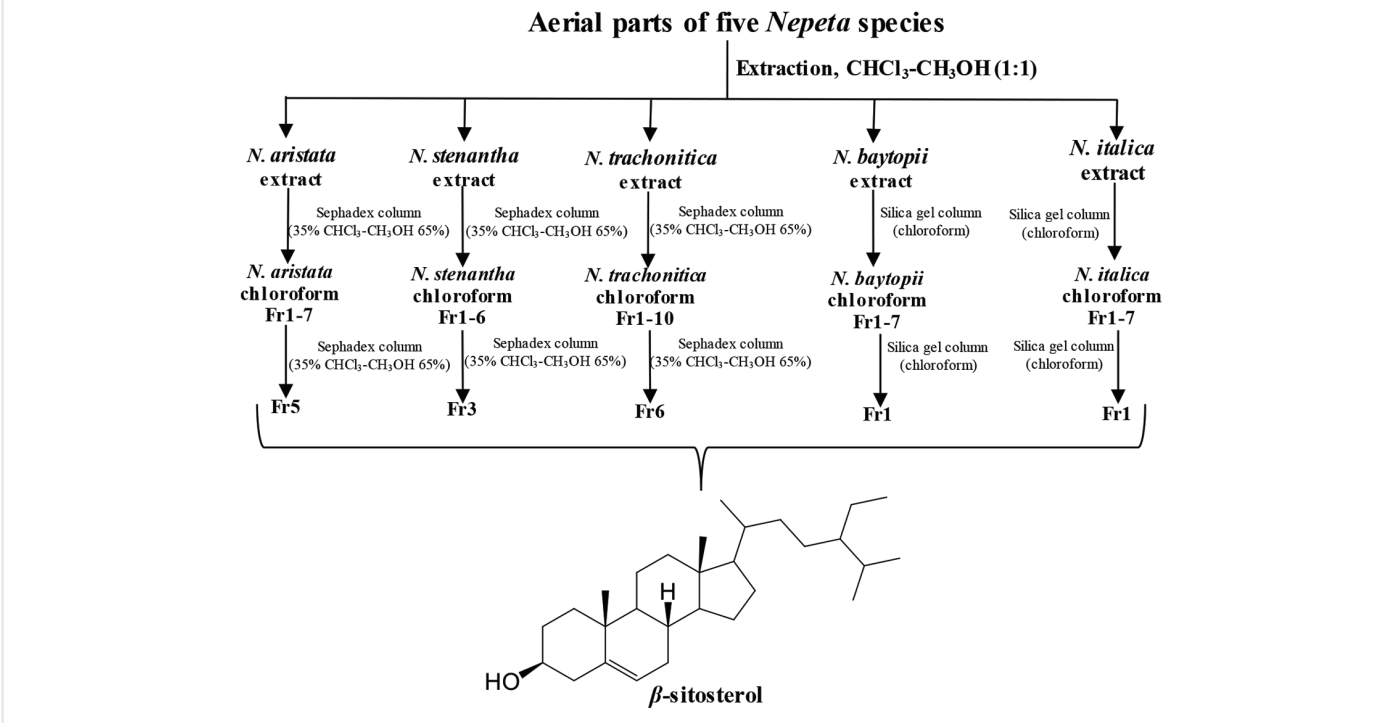

Figure 1. Scheme of isolation of the β-sitosterol from five *Nepeta* species

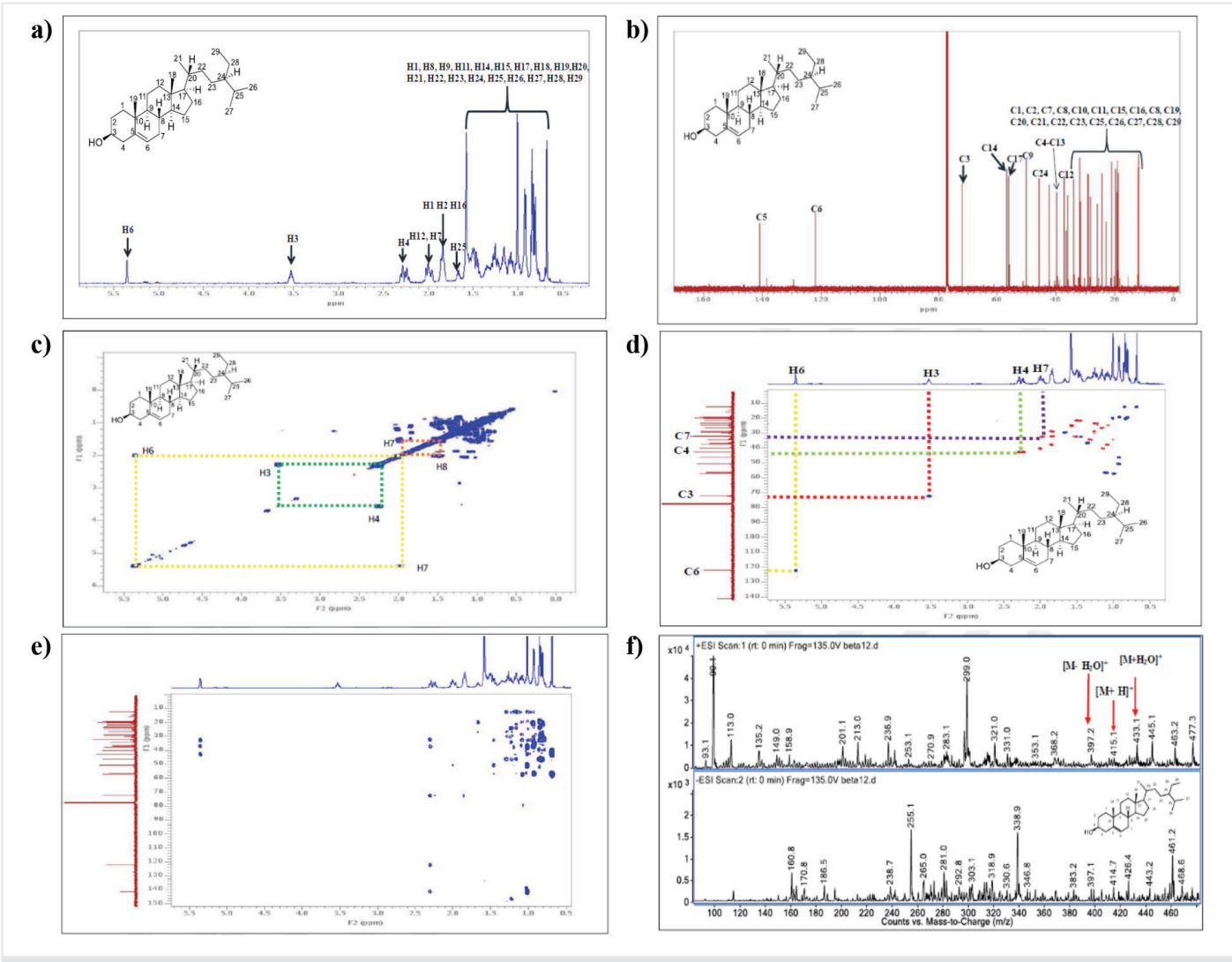

Figure 2. a) ^{1}H-NMR (CD_3OD, 600 MHz), b) ^{13}C-NMR (CD_3OD, 150 MHz, c) COSY, d) HSQC, e) HMBC spectra, (f) MS spectra of the β-sitosterol

the active site of the urease enzyme (Supplementary Table 1 and Figure 4a). The interactions of the BS with urease, binding affinities, and constant (-7.50 kcal/mol and 3.86 μM) were calculated (Table 2).

Eight alkyl connections with ALA65, ILE91, VAL121, and LEU198, as well as six P-A contacts with HIS94, HIS96, and PHE131, were generated by BS, which interacts with the active region of the CA enzyme (Supplementary Table 2 and Figure 4b). The interactions of the BS with CA, binding affinities, and constant (-7.40 kcal/mol and 3.71 μM) were determined (Table 2).

The lipase enzyme's active site is where BS interacts. It was shown to form one P-A contact with HIS354, two carbon-hydrogen bonds with ASP272 and LYS268, four alkyl interactions with LYS268 and LEU356, and one conventional hydrogen bond with ASP272 (Supplementary Table 3 and Figure 4c). Interactions of BS with lipase, binding affinities, and constants (-7.00 kcal/mol and 11.54 μM) were calculated (Table 2).

According to Supplementary Table 4 and Figure 5a, BS interacts with the tyrosinase enzyme's active site by forming eight alkyl contacts with ALA228 and VAL300 and five P-A interactions with PHE239, TYR297, and PHE537. The interactions of the BS with tyrosinase, with a binding affinity and constant (-8.80 kcal/mol and 0.62 μM), were calculated (Table 2).

According to Supplementary Table 5 and Figure 5b, BS interacts with the α-amylase enzyme's active site by forming one hydrogen bond with ALA3, nine alkyl contacts with ALA3, LEU211, ARG227, PRO228, ILE230, and LYS208, and one P-A interaction with TYR2. The interactions of the BS with α-amylase to have a binding affinity and constant (-8.90 kcal/mol and 0.53 μM), were calculated (Table 2).

Supplementary Table 6 and Figure 5c show that BS interacts

Table 1. ^{1}H- and ^{13}C-NMR data and literature values of the β-sitosterol

No	^{1}H-NMR ((CD_3OD, 600 MHz)	^{13}C-NMR (CD_3OD, 150 MHz)	^{1}H-NMR (22)	^{13}C-NMR (22)
1	1.07-1.84 (m)	37.23	1.46 (m)	37.28
2	1.50-1.83 (m)	31.64	1.56 (m)	31.69
3	3.51	71.8	3.54	71.82
4	2.25-2.28 (m)	42.28	2.32 (m)	42.33
5	-	140.70	-	140.77
6	5.34	121.25	5.37	121.73
7	1.97	31.9	2.04	31.93
8	1.44	31.88	1.69	31.93
9	0.93	50.1	1.55	50.16
10	-	36.49	-	36.51
11	1.48	21.07	1.52	21.11
12	1.15-1.99 (m)	39.75	1.51 (m)	39.80
13	-	42.30	-	42.34
14	0.98	56.75	1.50	56.79
15	1.57	24.29	1.58	24.33
16	1.83	28.24	1.85	28.27
17	1.1	56.02	1.45	56.08
18	0.84	11.85	0.7	11.89
19	1.0	19.39	1.03	19.42
20	1.35	36.13	1.6	36.17
21	0.91	18.77	0.94	18.84
22	1.0-1.31 (m)	33.92	0.93 (m)	33.98
23	1.15	26.02	1.15	26.11
24	0.92	45.80	1.38	45.86
25	1.65	29.11	1.57	29.19
26	0.82	19.82	0.84	19.84
27	0.8	19.01	0.86	19.06
28	1.21-1.26 (m)	23.04	1.12 (m)	23.10
29	0.67	11.97	0.82	12.01

NMR: Nuclear magnetic resonance

with the active site of the α-glucosidase enzyme by forming one alkyl contact with PRO82 and one P-A interaction with TRP81. The interactions of the BS with α-glucosidase, with a binding affinity and constant of -8.00 kcal/mol and 2.27 μM, were calculated (Table 2).

Molecular Dynamics (MD) Simulations

In drug development methods, analyzing the dynamic behavior of molecules and the complex systems in which these molecules interact is indispensable. MD simulation is one of the calculations made in a computer environment. MD simulations enable the determination of flexibility in targets that traditional molecular docking techniques cannot. This way, the calculated binding energies can provide more accurate information about potential inhibitors (24).

Since it was observed that BS had the best interaction with tyrosinase in our molecular docking studies, enzyme kinetics, and inhibition studies, an MD simulation was performed on the complex it formed with tyrosinase. RMSD, RMSF, Rg values, and H-bonds were utilized in MD simulations to assess the stability of BS under physiological conditions in the presence of tyrosinase. From the RMSD plots, the complexes remained stable for 100 ns at approximately 4-4.5 nm (Figure 6a). During the simulation, RMSF calculates the changes in amino acid residues in the absence of ligand molecules. According to Figure 6b, the calculated RMSF values for tyrosinase indicate that the intensity of the fluctuation ranges from 0.05 to 0.40 nm. The H-bonds generated by the complexes at 100 ns in the MD simulation are shown in Figure 6c. The MD simulation showed that one to three H-bonds interacted in both complexes.

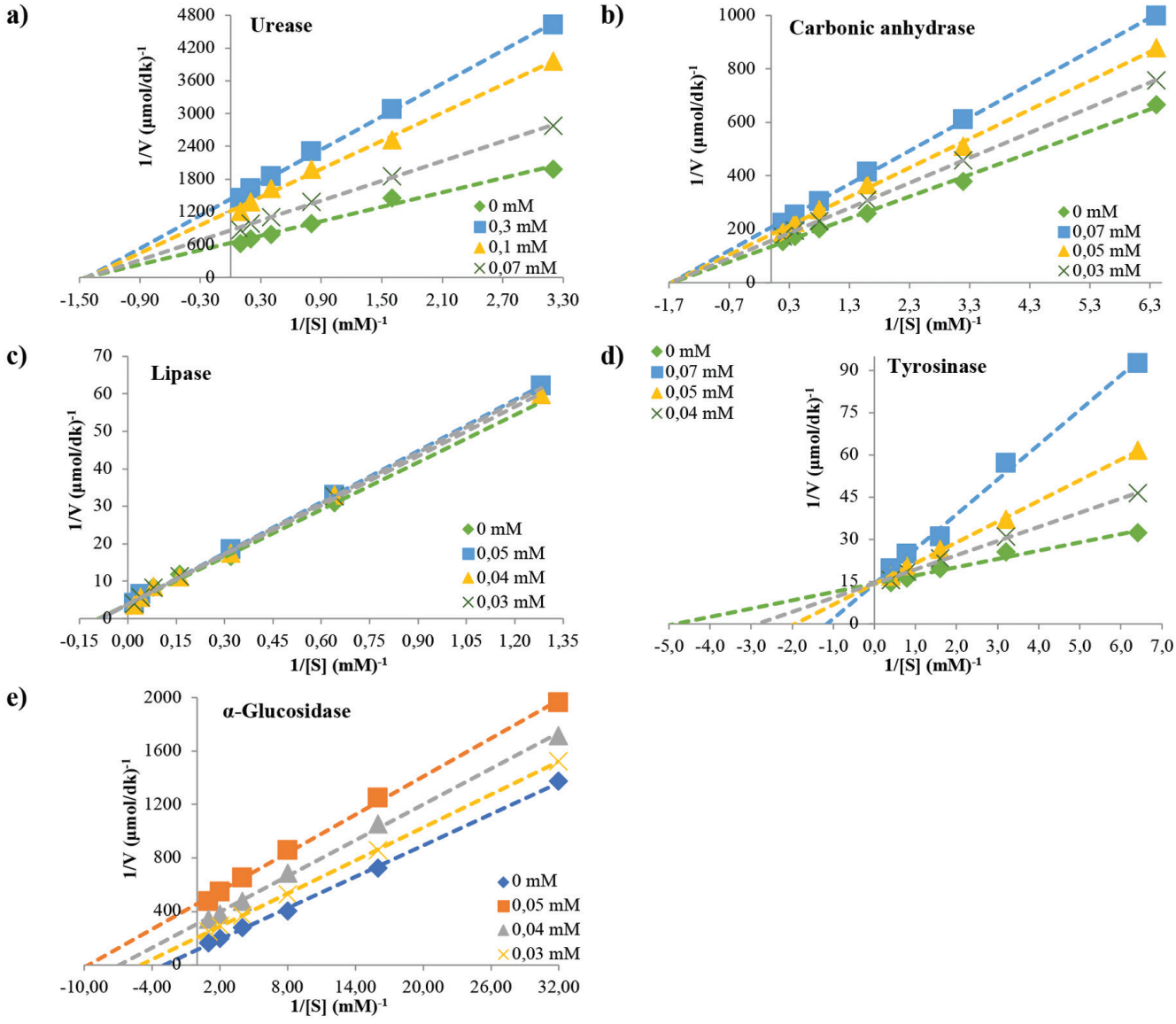

Figure 3. Lineweaver-Burk plots of a) urease, b) carbonic anhydrase, c) lipase, d) tyrosinase, and e) α-glucosidase for β-sitosterol

Rg shows the loose molecular packing of a protein and is a valuable and accurate indicator of a drug's ability to alter protein structure. The dynamic calculation for 100 ns in Figure 6d shows that tyrosinase and BS are coherent at about 2.40 and 0.50 nm.

MM/PBSA analysis

The binding free energy may be found using MM/PBSA, one of the most commonly used methods. One can expect that a ligand-protein combination is more stable and has more ligand activity and potency if its estimated free binding energy is lower. Protein-ligand complexes' free binding energy ($\Delta G_{binding}$) was assessed using MM-PBSA. The energy contributions are G_{GAS} and G_{SOLV}, and MM-PBSA is ranked using the binding energy parameters. E_{GB} and E_{SURF} are the polar and non-polar contributions, according to the GB estimations in Table 3. Despite the considerable electrostatic contribution of all mutations, the van der Waals term is the primary contributor to the overall binding free energy, as it is significantly offset by a large positive polar contribution (E_{GB}). The overall polar contribution (E_{EL}+E_{GB}) is thus positive (25). The complexes' ΔG binding values for tyrosinase are -4.39 kcal/mol, as shown in Figure 6e. An examination of the MM-PBSA data showed that the van der Waals contact force is far more significant than the electrostatic force in protein-ligand interaction. The MD simulation's output parameters and the docking findings exhibit a significant correlation, suggesting that the docked protein-ligand complexes remain stable during the simulation.

Table 2. Enzyme inhibitions, inhibition types, binding affinities and constants of *β*-sitosterol

Enzymes	β-sitosterol	Standard drugs	Inhibition types	Inhibitor constant (K_i, μM)	Binding affinity (kcal/mol)	Binding constant (K_i, μM)
	IC_{50} (μM)					
Urease	21.60±0.01	130.98±0.00 (Thiourea)	Non-competitive	335.55	-7.50	3.86
CA	67.70±0.01	10.57±0.27 (Acetazolamide)	Non-competitive	203.40	-7.40	3.71
Lipase	42.50±0.02	12.71±2.04 (Orlistat)	Competitive	1032.22	-7.00	11.54
Tyrosinase	6.60±0.02	181.76±11.12 (Kojic acid)	Competitive	37.35	-8.80	0.62
α-amylase	280.09±0.00	40.16±0.25 (Acarbose)	-	-	-8.90	0.53
α-glucosidase	274.64±6.80	20.91±0.06 (Acarbose)	Uncompetitive	25.67	-8.00	2.27

IC_{50}: Half-maximal drug inhibitory concentration, K_i: Inhibitor constant, CA: Carbonic anhydrase

Discussion

Enzyme Inhibitions and Kinetic Assays

In the literature search, no references were found to compare the inhibition and inhibition kinetics of urease, CA, and lipase. For this reason, the study on these enzymes will be the first. In previous studies, the α-amylase inhibition of BS was found to be 0.21±0.01 mmol ACAE/g IC_{50} value of 154.40±15.80 μg/mL (26), and an IC_{50} value of 55.25 μg/mL (27). In another study, the inhibition of α-amylase by BS could not be determined (28). When the results in the literature are compared with those in our study, the α-amylase inhibition in our study is lower.

Sheng et al. (27) determined the type of α-amylase inhibition by BS as semi-competitive and the K_i value as 5.51 μg/mL.

In previous studies, the α-glucosidase inhibition of BS was found to be 14.69±0.15 mmol ACAE/g (29), an IC_{50} value >100 μg/mL Salah El Dine et al. (30), and an IC_{50} value of 283.67 μg/mL (27). In another study, α-glucosidase inhibition of BS could not be determined (28). The results of our investigation indicate a lower level of α-glucosidase inhibition compared to those reported in the literature.

Sheng et al. (31) determined that the inhibition type of α-glucosidase by BS was competitive, with a K_i value of 20.09 mg/L. In contrast, another study by Sheng et al. (27) determined that the inhibition type of α-glucosidase by BS was non-competitive, with a K_i value of 20.09 μg/mL.

In previous studies, the tyrosinase inhibition of BS was found to be 8.10±0.24 mg KAE/g (26), 73.42±1.67 mg KAE/g (29), 73.42±1.67 mg KAE/g (32), and in another study, the tyrosinase inhibition of BS could not be determined (33).

Molecular Docking

Quek et al. (26) calculated the binding energy of the BS-α-amylase interaction as -9.30 kcal/moL. In our study, the binding energy of the BS-α-amylase interaction was observed to be higher. Hasan et al. (34) determined the docking score of the BS-α-amylase interaction as -3.21, and Purnomo et al. (35) calculated the binding energies of the α-amylase and α-glucosidase interaction of BS as -8.66 and -9.59 kcal/mol. In our study, the binding energy of the BS-α-amylase interaction was lower, whereas the binding energy of the α-glucosidase interaction was higher. Mandar et al. (36) found the binding energies of the α-amylase and α-glucosidase interactions with BS to be -9.30 and -8.50 kcal/mol, respectively. In our study, the binding energies of the α-amylase and α-glucosidase interaction of BS were observed to be higher. In the study conducted by Shanak et al. (37), the binding energies of the interaction of BS with α-amylase and α-glucosidase were observed as -8.38 kcal/mol, -7.93 kcal/mol, and the binding constants as 719.79 nM, 1.53 μM. In our study, the binding energies of the interaction of BS with α-amylase and α-glucosidase were observed to be lower. Sari et al. (38) determined the binding energy of the interaction of BS and α-glucosidase as -10.61 kcal/mol. In our study, the binding energy of the interaction of BS-α-glucosidase was determined to be lower.

Study Limitations

The fact that there are many previous enzyme inhibition studies on BS is a limitation of this study.

Conclusion

Our study investigated the enzyme inhibition activities and kinetics of BS isolated from five different *Nepeta* species (*N. aristata, N. italica, N. baytopii, N. stenantha,* and *N. trachonitica*). In addition, the molecular structure of BS was determined using NMR, and its mass was determined using MS. It was recorded that BS had high urease and tyrosinase inhibition. The enzyme inhibition kinetics of BS with urease, CA, lipase, tyrosinase, α-amylase, and α-glucosidase were investigated, and the inhibitory constant formed by urease and tyrosinase was high. Upon examining the molecular docking, it was observed that α-amylase exhibited the highest binding affinity among the six enzymes. Considering these results, the MD simulation of BS with tyrosinase was investigated. It was observed to be stable at 4 nm for 100 ns in the RMSD graph. Additionally, the binding energy was calculated to be -4.39 kcal/mol using MM/PBSA analysis. Thus, it is likely to play a leading role in the use of cosmetics and drugs.

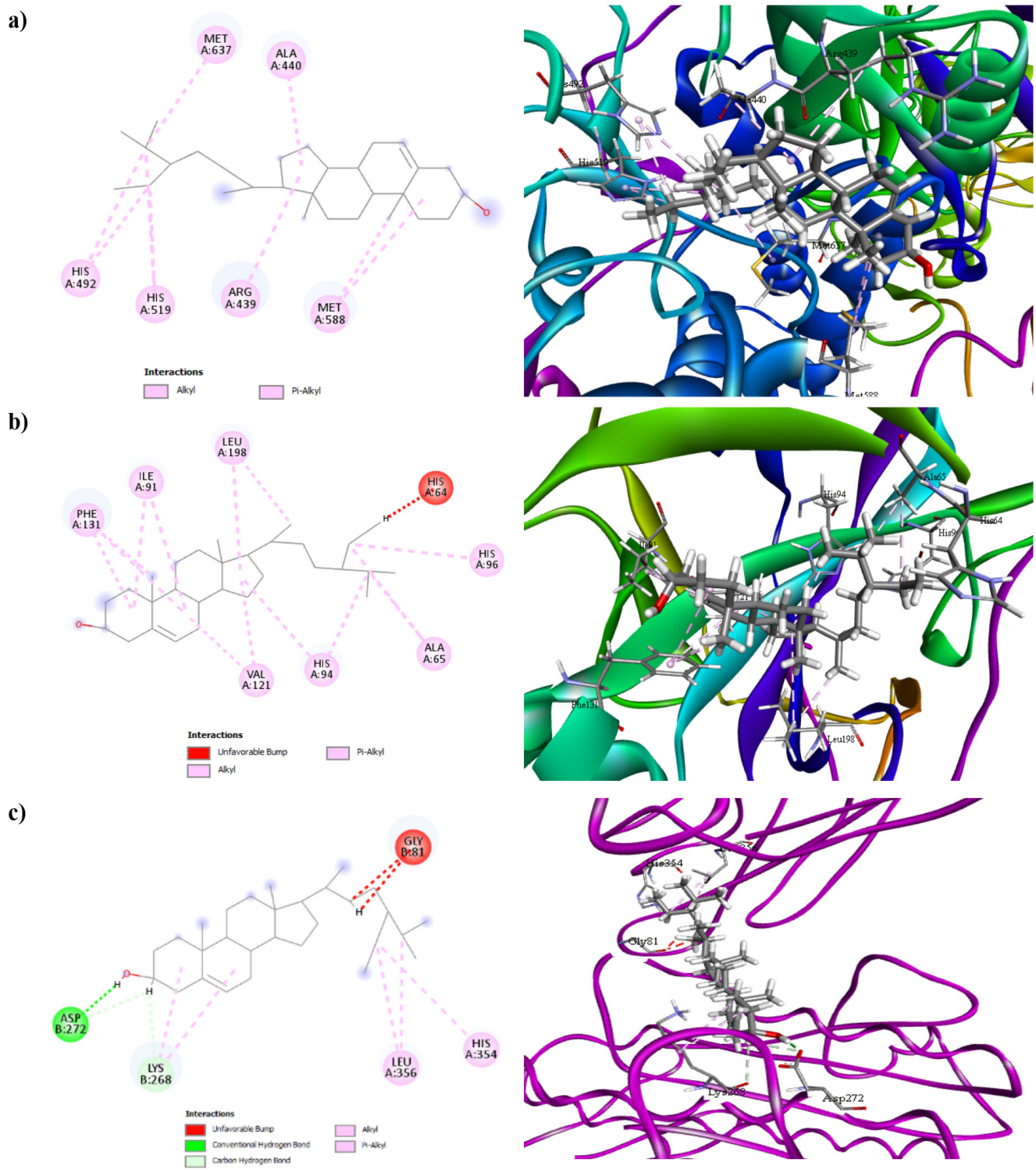

Figure 4. Molecular docking 2D and 3D images of the β-sitosterol a) urease, b) CA, and c) lipase

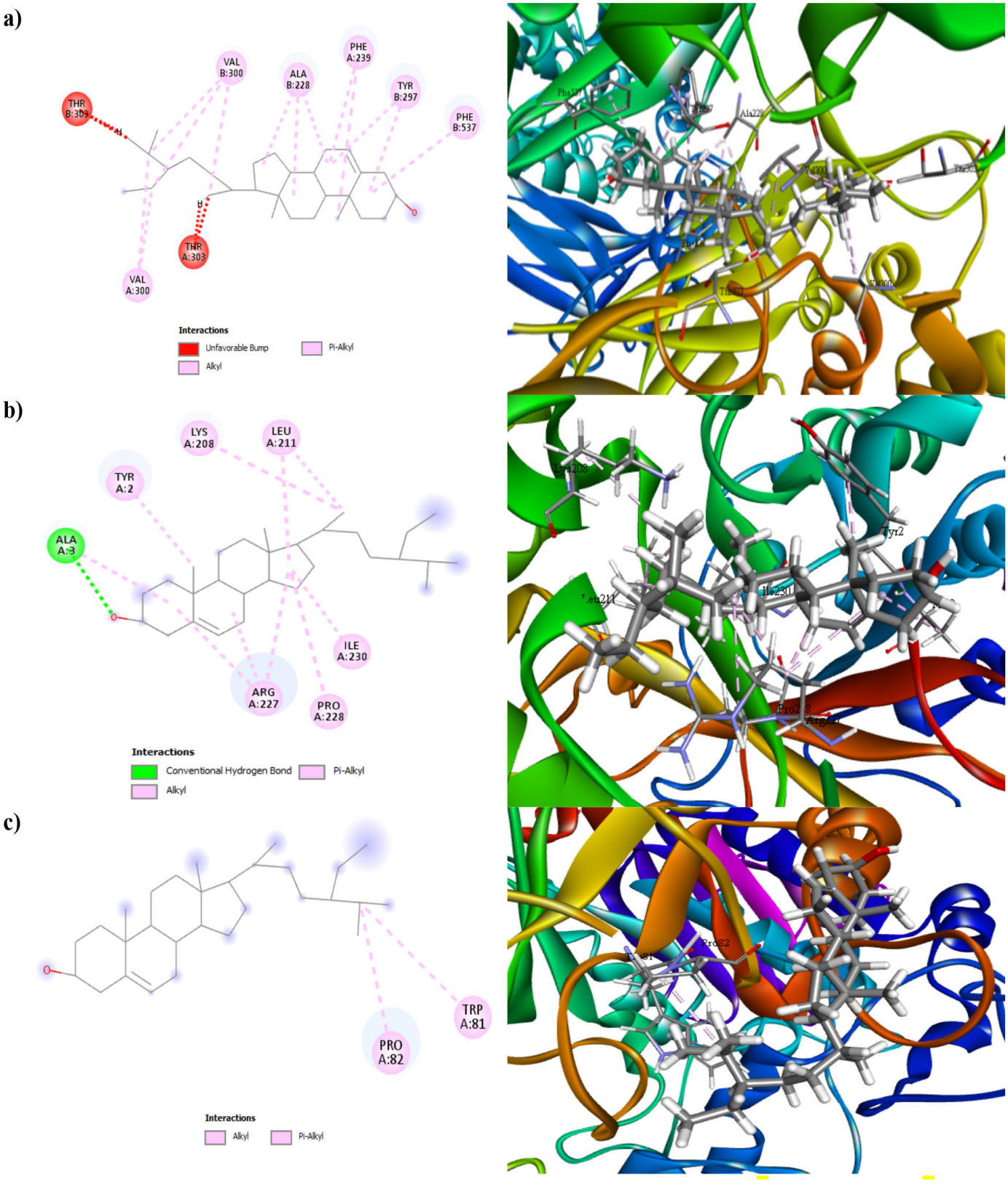

Figure 5. Molecular docking 2D and 3D images of the β-sitosterol a) tyrosinase, b) α-amylase, and c) α-glucosidase

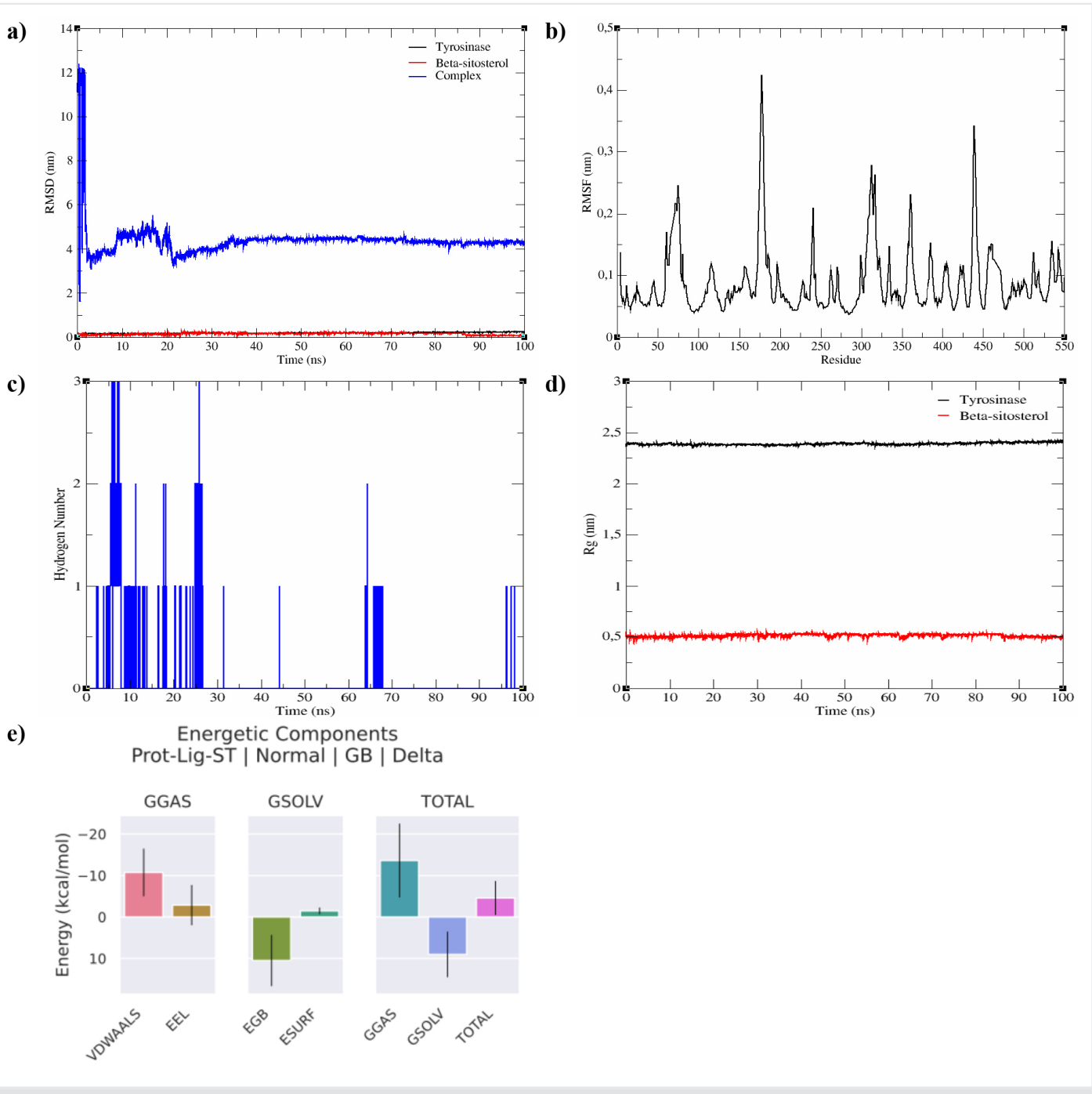

Figure 6. a) RMSD and b) RMSF, c) H-bond interactions, d) Rg plotting, e) MM-PBSA energy with tyrosinase

RMSD: Root mean square deviation, RMSF: Root-mean-square fluctuation, Rg: Radius of gyration, E_{EL}: Electrostatic energy as calculated by the MM force field, E_{GB}: The electrostatic contribution to the solvation-free energy calculated by GB, E_{SURF}: Hydrophobic contribution to solvation-free energy for GB calculations, G_{SOLV}: Sum of nonpolar and polar contributions to solvation, G_{GAS}: Total gas phase energy (ELE+VDW+INT)

Table 3. MM/PBSA energy results of the complex

Compounds	VDW	E_{EL}	E_{GB}	E_{SURF}	ΔG_{GAS}	ΔG_{SOLV}	$\Delta G_{binding}$
β-sitosterol-tyrosinase	-7.21±6.92	-7.71±10.03	11.73±11.87	-1.20±1.17	-14.93±15.52	10.54±10.82	-4.39±5.13

MM/PBSA: Molecular mechanics Poisson-Boltzmann surface area, VDW: Van der Waals contribution from MM, E_{EL}: Electrostatic energy as calculated by the MM force field, E_{GB}: The electrostatic contribution to the solvation-free energy calculated by GB, E_{SURF}: Hydrophobic contribution to solvation-free energy for GB calculations, ΔG_{GAS}: Total gas phase energy (ELE+VDW+INT), ΔG_{SOLV}: Sum of non-polar and polar contributions to solvation, $\Delta G_{binding}$: Final estimated binding free energy calculated from the terms above (kcal/mol)

Ethics

Ethics Committee Approval: Not obtained, as no animals or humans were used in the study. Additionally, our study does not require approval from an ethics committee.

Informed Consent: Not obtained, as no patients were involved in the study. Additionally, our study does not require patient consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.Y., Y.B., I.D., T.O., Concept: S.Y., Y.B., Y.I., I.D., T.O., L.B., Design: S.Y., Y.B., Y. I., I.D., T. O., L.B., Data Collection or Processing: S.Y., Y.B., I.D., T.O., Analysis or Interpretation: S.Y., Y.B., Y. I., I.D., T.O., Literature Search: S.Y., Y.B., I.D., T.O., Writing: S.Y., Y.B., I.D., T.O.

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

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Supplementary Tables 1-6: https://d2v96fxpocvxx.cloudfront.net/bd1986e1-0bc1-4f4d-af66-3a184850a065/content-images/4f6b5280-110e-4a31-913f-3b2d7fd6bf95.pdf

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Original Article

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Comparative Efficacy of Letrozole and Clomiphene in Ovulation Induction for Infertile Females with Comorbidities: A Cross-sectional Study

Komorbiditesi Olan İnfertil Kadınlarda Ovulasyon İndüksiyonu için Letrozol ve Klomifenin Karşılaştırmalı Etkinliği: Kesitsel Bir Çalışma

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ABSTRACT

Objective: The primary objective of the study was to compare the efficacy of clomiphene and letrozole in inducing ovulation in infertile women with comorbidities. Secondary objectives included evaluating differences in pregnancy outcomes in terms of pregnancy rates, multiple gestation and adverse effects of the drugs between the two treatment groups.

Methods: A cross-sectional study was conducted at CMH Kharian Medical College and associated hospital from January to June 2025. A sum of 120 infertile women with varied comorbidities were enrolled and divided into two treatment groups: letrozole group and clomiphene group. The study estimated and statistically evaluated ovulation rates, pregnancy rates, multiple gestation and adverse effects of the drugs between the groups.

Results: The letrozole group demonstrated significantly better outcomes in terms of ovulation (86.7%) and pregnancy rates (66.7%) as compared to clomiphene group (68.3% and 40.0%, respectively). Letrozole was associated with fewer side effects and a lower prevalence of multiple gravidity (5.0%) as compared to clomiphene group (18.3%).

ÖZ

Amaç: Bu çalışmanın birincil amacı, komorbiditesi olan infertil kadınlarda ovulasyonu indüklemede klomifen ve letrozolün etkinliğini karşılaştırmaktı. İkincil amaçlar arasında, iki tedavi grubu arasında gebelik oranları, çoğul gebelik ve ilaçların yan etkileri açısından gebelik sonuçlarındaki farklılıkların değerlendirilmesi yer almaktadır.

Yöntemler: Ocak-Haziran 2025 tarihleri arasında CMH Kharian Tıp Fakültesi ve bağlı hastanede kesitsel bir çalışma yürütüldü. Komorbiditeleri farklılık gösteren toplam 120 infertil kadın çalışmaya dahil edilerek letrozol grubu ve klomifen grubu olmak üzere iki tedavi grubuna ayrıldı. Çalışmada ovulasyon oranları, gebelik oranları, çoğul gebelik ve ilaçların yan etkileri tahmin edilerek istatistiksel olarak değerlendirildi.

Bulgular: Letrozol grubu, ovulasyon (%86,7) ve gebelik oranları (%66,7) açısından klomifen grubuna (%68,3 ve %40,0) kıyasla anlamlı derecede daha iyi sonuçlar gösterdi. Letrozol, daha az yan etki ve daha düşük çoğul gebelik prevalansı (%5,0) ile ilişkilendirildi; klomifen grubunda bu oran %18,3 idi.

Sonuç: Letrozol, komorbiditesi olan infertil kadınlarda ovulasyon indüksiyonu açısından klomifen sitrata göre daha

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ABSTRACT

Conclusion: Letrozole appears to be more effective and safer than clomiphene citrate for ovulation induction in infertile women with comorbidities. Grounded on these findings, letrozole may be considered a first line treatment option in infertile women with comorbidities.

Keywords: Infertility, ovulation induction, letrozole, clomiphene, comorbidity, polycystic ovary syndrome

ÖZ

etkili ve daha güvenli görünmektedir. Bu bulgulara dayanarak; letrozol, bu hasta grubunda birinci basamak tedavi seçeneği olarak değerlendirilebilir.

Anahtar Kelimeler: İnfertilite, ovulasyon indüksiyonu, letrozol, klomifen, komorbidite, polikistik over sendromu

Introduction

Infertility is a major global health concern, with an estimated 17.5% of individuals worldwide suffering from it (1). Primary infertility, in which a person has never become pregnant, and secondary infertility, in which a person has failed to conceive despite having previously become pregnant, are the two main categories of infertility, which is defined as the inability to conceive after 12 months of consistent and unprotected sexual activity (2). Among several reasons of infertility, ovulatory dysfunction, notably disruptions in the hypothalamic-pituitary-ovarian axis, is a significant factor influencing female fertility. Obesity, metabolic syndrome, thyroid issues, and polycystic ovarian syndrome (PCOS) are major causes of anovulation, which can interfere with fertility treatment and diminish the chances of a healthy pregnancy (3,4).

Clomiphene citrate (CC) has long been the first-line treatment for ovulation induction medications. Clomiphene, a selective estrogen receptor modulator, stimulates the synthesis of gonadotropin, which encourages follicular growth and ovulation (5). Nevertheless, CC has a number of drawbacks despite its proven clinical application, such as poor live birth rate, increased risk of multiple pregnancies (3-8%), and notable response variability among people with metabolic problems (6). However, common adverse effects include stomach spasms, breast tenderness, hot flushes, and thrombosis-related effects, and it also shows effects like multi-follicular development and cyst formation (7). As a result, alternative forms of treatment have been studied. A third-generation aromatase inhibitor called letrozole (LE) is one such choice. It has been demonstrated to have superior ovulation and pregnancy results versus CC, particularly in individuals with comorbidities (8). LE promotes follicle-stimulating hormone secretion and follicular recruitment by reducing estrogen production, hence preventing negative feedback inhibition at the hypothalamus level (9,10). LE is less likely to cause mood and vasomotor adverse effects than CC (11).

Despite advancements in the treatment of infertility, comorbidities like as insulin resistance, obesity, thyroid problems, hypertension, and fibroids remain significant barriers to successful reproduction. Both directly and indirectly, these disorders affect ovarian function and implantation potential (12,13). Despite several studies have compared LE to CC, highlighting its usefulness in PCOS patients, there is little evidence on LE's effectiveness in infertile women with numerous comorbidities. To improve evidence-based clinical treatment, a focused assessment of ovulation induction drugs in various patients' groups is required.

The purpose of this study is to thoroughly evaluate the effectiveness of LE and CC in stimulating ovulation leading to conception in infertile women with gynecological and systemic comorbidities. In addition to offering therapeutically useful insights on refining ovulation induction procedures for patients with underlying comorbidities, this study seeks to deepen our understanding of the pharmacology of ovulation induction agents.

Methods

Study Design

Cross-sectional analytical (observational) study.

Study Setting

CMH Kharian Medical College and CMH Hospital, Kharian, Pakistan.

Ethical Approval

Approval obtained from Institutional Ethical Review Board, CMH Kharian Medical College (approval no: CKMC/IERB/AC-00202, date: 09.01.2025), written informed consent obtained from all participants, confidentiality and anonymity ensured.

Sample Size

Sample size was calculated to be 57 with the help of World Health Organization calculator taking ovulation rate with the use of LE as 61.1% and clomiphene as 35%, and keeping power of the study at 80%. After adjusting drop out ratio of 5% (n=3), sample size of 60 was finalized. The sample size determination process is shown in Figure 1.

Sampling Technique

Non-probability consecutive sampling.

Participants

One hundred-twenty infertile women with comorbidities.

Treatment Details

Treatment plans were modified depending on clinical judgment because this was an observational cross-sectional study and they were not standardized. The patients had previously received treatment for their infertility with LE or CC. The number of treatment cycles and dosages varied from participant to participant, as is customary in therapeutic practice. The majority of patients began on a starting dose of either 50 mg/day of CC or 2.5 mg/day of LE for five days per cycle; however, treatment durations and dosage modifications varied based on patient response and medical interpretation.

Inclusion Criteria

Women aged 18-40 years with infertility and comorbidities such as PCOS, obesity, thyroid dysfunction, diabetes, hypertension, or fibroids.

Exclusion Criteria

Women with structural infertility, male factor infertility, or infertility without comorbidities.

Treatment Exposure and Clinical Decision-making

Observational design, treatment not assigned or modified by investigators, patients already receiving CC or LE at enrollment, therapy selected by treating physician as part of routine clinical practice, clomiphene commonly used as first-line agent, LE more frequently prescribed in suspected or documented CC resistance, PCOS, higher body mass index, or prior inadequate ovulatory response, no protocol-driven treatment allocation.

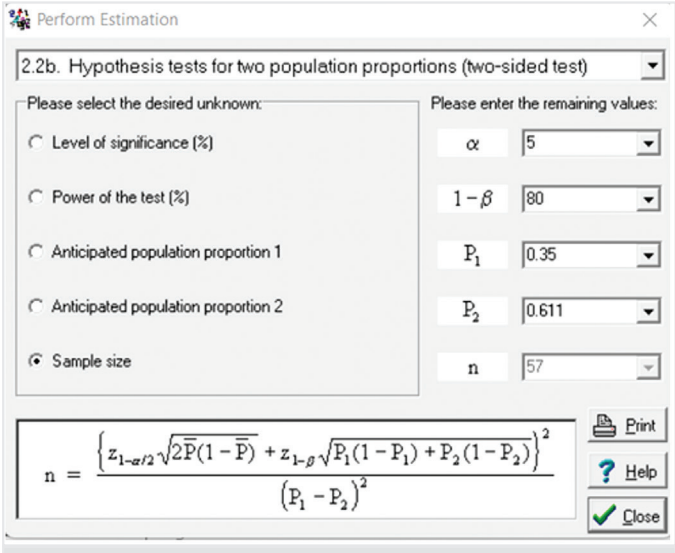

Figure 1. Screenshot of the World Health Organization sample size calculator displaying inputs used for this study: alpha: 5%, power: 80%, P1: 0.35, P2: 0.611, resulting in estimated sample size of 57 participants per group

Data Collection

Questionnaire, lab investigations and ultrasound record.

Outcomes Measured

Transvaginal ultrasound was used to confirm ovulation, and biochemical indicators such as beta human chorionic gonadotrophin hormone levels, urine pregnancy test, or ultrasound imaging were used to confirm pregnancy.

Statistical Analysis

SPSS version 20 was used to examine the data. For demographic factors, descriptive statistics were used. Results were compared between groups using independent t-tests and chi-square tests. Statistical significance was established at $p<0.05$ and a 95% confidence range was employed.

Results

The study comprised 120 infertile women with either comorbidity, 60 in each group. Both groups had comparable baseline characteristics, including mean age and duration of infertility, with no statistically significant differences found (Table 1). The study design and participant allocation are illustrated in Figure 2.

The distribution of comorbidities between the two groups is shown in Table 2. The most common comorbidity was PCOS, which affected 26 (43.3%) participants in the CC group and 25 (41.7%) in the LE group. Other comorbidities included hypothyroidism, diabetes, hypertension, fibroids, and depression, which varied in prevalence between groups.

Regarding treatment results, a substantially higher percentage of patients in the LE group (n=52; 86.7%) had

Table 1. Demographic characteristics of participants

Variable	Group 1 (clomiphene citrate)	Group 2 (letrozole)	p-value
Age (years)	29.28±3.26*	28.78±5.02*	0.519
Infertility duration (years)	4.04±1.89*	4.37±2.26*	0.392

*: Values are presented as mean ± standard deviation

Table 2. Distribution of comorbidities among groups

Comorbidity	Group 1 (clomiphene citrate) n=60	Group 2 (letrozole) n=60
PCOS	n=26 (43.3%)*	n=25 (41.7%)*
Hypothyroid	n=12 (20.0%)*	n=6 (10.0%)*
Diabetes	n=8 (13.3%)*	n=5 (8.3%)*
Hypertension	n=3 (5.0%)*	n=10 (16.7%)*
Fibroid	n=0 (0.0%)*	n=4 (6.7%)*
Depression	n=0 (0.0%)*	n=1 (1.7%)*

*: Data shown as number of patients with percentage in parentheses, PCOS: Polycystic ovarian syndrome

ovulation than in the CC group (n=41; 68.3%), with a p-value of 0.016. Likewise, with a p-value of 0.003, the LE group had a greater pregnancy rate (n=40; 66.7%) than the CC group (n=24; 40.0%) (Table 3).

There was a statistically significant difference (p=0.023) in the frequency of multiple gestations between the CC group (n=11; 18.3%) and the LE group (n=3; 5.0%).

Table 4 details the incidence of adverse effects. A considerably higher proportion of individuals in the LE group (68.3%) reported no side effects than those in the CC group (35.0%).

Discussion

LE's and CC's relative effectiveness in triggering ovulation has been a key topic of discussion when treating infertile women, particularly those with coexisting conditions like PCOS. Since LE is more effective than CC at inducing ovulation, it is advised for patients with PCOS and related conditions (3,14).

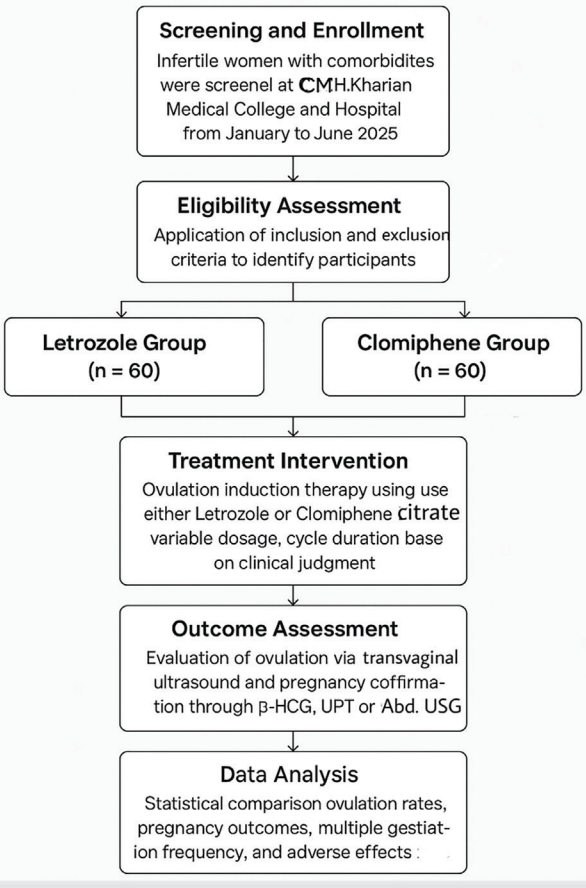

Figure 2. Flow diagram illustrating the study design, patient screening, group allocation, treatment intervention, and analysis

HCG: Human chorionic gonadotrophin, UPT: Urine pregnancy test

CC has been used for a long time most often as first-line drug for ovulation induction. However, current professional recommendations and research have progressively favored LE, particularly in women with PCOS and other metabolic disorders, due to better ovulatory and pregnancy outcomes. Despite this shift in preference, resistance to both agents remains a significant barrier to fertility management, particularly in low-resource settings where assisted reproductive technologies are less affordable.

Our results are consistent with recent research showing that LE is more effective than clomiphene at inducing ovulation and improving pregnancy outcomes. The current study found that LE significantly increased the rate of conception (66.7%) compared to CC (40%) in infertile women with a variety of comorbidities, including PCOS, obesity, thyroid, and metabolic abnormalities. Our findings are in line with a randomized control experiment that showed that LE had a 62% pregnancy rate and CC had a 38% pregnancy rate (15).

Similarly, LE was associated with significantly greater clinical pregnancy [odds ratio (OR)≈1.69] and live-birth (OR≈1.72) rates than clomiphene in a 2022 Cochrane meta-analysis of PCOS patients (16).

Comorbidities are also important since they lower fertility and interfere with folliculogenesis. Most common being obesity, insulin resistance, and metabolic syndrome. CC significantly reduces live birth rates in women with metabolic syndrome, whereas LE proves comparatively better outcomes in this group, according to analyses from major trials (12). Thyroid autoimmunity and obvious hypothyroidism also impair menstrual cycles and pregnancy (13). Although specific data in thyroid or diabetes affected patients is limited, our findings indicate that LE's pharmacological profile may better overcome such challenges.

Table 3. Treatment outcomes

Outcome	Group 1 (clomiphene citrate) n=60	Group 2 (letrozole) n=60	p-value
Ovulation rate	n=41 (68.3%)*	n=52 (86.7%)*	0.016
Pregnancy rate	n=24 (40.0%)*	n=40 (66.7%)*	0.003
Multiple gestation rate	n=11 (18.3%)*	n=3 (5.0%)*	0.023

*: Data presented as number of patients with percentage in parentheses, statistical significance at p<0.05

Table 4. Adverse effects

Adverse effect status	Clomiphene citrate group (n=60)	Letrozole group (n=60)
No adverse effects	n=21 (35.0%)*	n=41 (68.3%)*
One or more side effects	n=39 (65.0%)*	n=19 (31.7%)*

*: Data shown as number of patients with percentage in parentheses

By specifically assessing ovulation induction in a sample of infertile women with a variety of gynecologic and systemic comorbidities such as hypothyroidism, hypertension, and fibroids in addition to PCOS, our study contributes to the field of current literature. This study offers a more comprehensive understanding of how LE and CC function in more complicated, real-life circumstances, in contrast to the majority of earlier research that concentrated largely on PCOS alone. Furthermore, our geographic context focuses on treatment patterns and outcomes in the South Asian community, where data on infertility therapy in the presence of comorbidities is limited.

To summarize, while CC achieved pregnancies in a large percentage of instances and remains a cost-effective alternative, the collective evidence, including our data, suggests an apparent efficacy advantage of LE for ovulation induction in infertile women with comorbidities (15,17). Infertile women with metabolic comorbidities should select LE as their first-line treatment; although more research is needed to confirm these results.

Considering the higher pregnancy rates with LE, clinicians ought to recommend it as a first-line ovulation induction medicine in infertile women with comorbidities, in compliance with changing clinical guidelines. CC is still a viable choice, especially in resource-constrained situations or for patients allergic to LE. However, patient selection should take into account comorbidities, prior treatment outcomes, and hormonal indicators. Comorbidity management (such as metabolic and thyroid optimization) paired with pharmacological ovulation stimulation may improve reproductive outcomes even more.

Study Limitations

To determine the effectiveness of treatment within each subgroup, future studies should stratify people according to particular comorbidities such PCOS, hypothyroidism, obesity, and insulin resistance. LE's advantage needs to be confirmed by randomized controlled studies with larger sample sizes and live birth outcomes. The clinical significance of these results would also be enhanced by long-term follow-up research on maternal and neonatal outcomes.

Conclusion

Comorbid conditions such as PCOS, hypothyroidism, diabetes, hypertension, and fibroids have been proven to reduce female fertility by interfering with hormonal balance, ovulatory function, and endometrial sensitivity. These illnesses typically hinder ovulation induction, lowering the likelihood of pregnancy in affected women.

In this case, pharmaceutical medicines like CC and LE are essential for inducing ovulation. Both medications are commonly used to treat anovulatory infertility; however, their efficacy varies depending on the underlying metabolic or endocrine problems. Our data revealed that LE resulted in considerably higher ovulation (86.7%) and conception rates (66.7%) than CC (68.3% and 40.0%, respectively), particularly in women with comorbidities. This indicates that LE may be more effective in overcoming the ovulatory problems posed in such conditions.

These findings are consistent with prior research showing that LE improves ovulatory and pregnancy outcomes, particularly in patients with PCOS and metabolic syndrome. For example, significant clinical trials have demonstrated that LE continues to provide positive results in women with metabolic dysfunction, whereas CC may be associated with lower live-birth rates in this group.

Moreover, LE was associated with fewer adverse effects, with a higher proportion of subjects claiming no side effects during therapy, indicating superior tolerance than CC.

In conclusion, despite the fact that this was not a cohort trial, the findings strongly supported LE over CC for ovulation induction in infertile women with accompanying diseases. LE appears to have both increased efficacy and improved tolerability, making it a better option in this patient population.

Ethics

Ethics Committee Approval: Approval obtained from Institutional Ethical Review Board, CMH Kharian Medical College (approval no: CKMC/IERB/AC-00202, date: 09.01.2025).

Informed Consent: Written informed consent obtained from all participants, confidentiality and anonymity ensured.

Footnotes

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

Authorship Contributions

Surgical and Medical Practices: S.R., M.K., Concept: A.L., Design: A.L., U.N., U.F., Data Collection or Processing: S.R., J.K., M.K., Analysis or Interpretation: A.L., U.N., S.R., J.K., F.K., Literature Search: A.L., U.N., S.R., J.K., F.K., U.F., Writing: A.L., F.K., U.F.

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

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Original Article

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Evaluation of Edible Mushroom *Cantharellus lutescens* as Potential Cholinesterase Inhibitors

Yenilebilir Mantar *Cantharellus lutescens*'in Kolinesteraz İnhibitörü Potansiyelinin Değerlendirilmesi

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ABSTRACT

Objective: Alzheimer's disease is one of the most common forms of dementia which affects the cognitive, physical, psychological, and social functions of individuals. Cholinesterase enzymes are known to play a pivotal role in the occurrence and progression of Alzheimer's disease. This study aims to evaluate the anticholinesterase and butyrylcholinesterase inhibitory activities of the mushroom *Cantharellus lutescens*, which can be found in İstanbul and its surrounding regions.

Methods: Extracts of *Cantharellus lutescens* mushroom were prepared by maceration with hexane, ethyl acetate, and methanol at room temperature. Acetylcholinesterase and butyrylcholinesterase inhibitory activities of these three extracts were determined using the Ellman method.

Results: While *Cantharellus lutescens* hexane extract was determined as the most active extract with 48.07±0.51% acetylcholinesterase inhibition at a concentration of 800 µg/mL, ethyl acetate extract showed the highest activity against butyrylcholinesterase with 29.20±0.80% inhibition at the same concentration.

Conclusion: This study evaluates the anticholinesterase activity of an edible mushroom that could be a potential therapeutic agent in the future.

Keywords: *Cantharellus lutescens*, yellow foot, anticholinesterase, Alzheimer's disease

ÖZ

Amaç: Alzheimer hastalığı, bireylerin bilişsel, fiziksel, psikolojik ve sosyal işlevlerini etkileyen en yaygın demans türlerinden biridir. Kolinesteraz enzimlerinin Alzheimer hastalığının ortaya çıkışında ve ilerlemesinde kritik bir rol oynadığı bilinmektedir. Bu çalışma, İstanbul ve çevresinde yetişen *Cantharellus lutescens* mantarının antikolinesteraz ve bütirilkolinesteraz inhibitör aktivitelerinin değerlendirilmesini amaçlamaktadır.

Yöntemler: *Cantharellus lutescens* mantarından hekzan, etil asetat ve metanol ile oda sıcaklığında maserasyon yöntemiyle ekstreler hazırlanmıştır. Bu üç ekstrenin asetilkolinesteraz ve bütirilkolinesteraz inhibitör aktiviteleri Ellman yöntemi ile belirlenmiştir.

Bulgular: *Cantharellus lutescens* hekzan ekstresi, 800 µg/mL konsantrasyonda %48,07±0,51 asetilkolinesteraz inhibisyonu ile en aktif ekstre olarak belirlenirken, etil asetat ekstresi aynı konsantrasyonda %29,20±0,80 bütirilkolinesteraz inhibisyonu ile en yüksek aktiviteyi göstermiştir.

Sonuç: Bu çalışma, gelecekte potansiyel bir terapötik ajan olabilecek yenilebilir bir mantarın antikolinesteraz aktivitesini değerlendirmektedir.

Anahtar Kelimeler: *Cantharellus lutescens*, sarı ayak, antikolinesteraz, Alzheimer hastalığı

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Introduction

Alzheimer's disease (AD), a progressive neurodegenerative disease, is the most prevalent form of dementia (1). According to the Alzheimer Europe report, more than 8 million individuals over the age of 30 were affected by AD in Europe and the USA in 2019, and this number is projected to double by 2050. Based on a survey of over 40,000 participants from 166 countries, conducted by London School of Economics (LSE) as a follow-up to ADI's 2019 survey, the new report examines how perceptions have evolved over five years. The World Alzheimer Report 2024 highlights widespread misconceptions and stigma around dementia. Many health professionals (65%) and the public (80%) wrongly see it as a normal part of ageing, and over a quarter believe it cannot be prevented. Nearly 90% of people with dementia experience discrimination, yet most carers and the public would pursue a diagnosis if treatments existed. Over 80% feel they can influence support through voting, and more than half link dementia to lifestyle factors (2).

Although there are many mechanisms associated with the occurrence of AD, cholinesterase enzymes seem to play a key role in the pathogenesis of the disease (2). Although drugs that exhibit cholinesterase inhibition are widely used as a treatment method, their administration is often associated with adverse side effects. Therefore, investigating the potential of natural products, such as mushrooms, against AD is of considerable importance. The number of studies targeting the anti-Alzheimer potential of mushrooms have been increasing in recent years supporting their involvement in different mechanisms to prevent or treat this neurodegenerative disease (3). *Cantharellus* species are edible mushrooms packed with micronutrients, trace elements and bioactive molecules. Their distinct apricot-like aroma makes them one of the top choices among consumers worldwide (4). A member of the *Cantharellus* genus*, Cantharellus lutescens (C. lutescens),* is commonly called "chick" or "chick"s leg mushroom". *C. lutescens* is characterized by its yellow stem, typically brown, drum-shaped cap and can be found in the forests of İstanbul almost all year long (5,6).

C. lutescens has previously been investigated for its thrombin inhibition activity (7) as well as for the influence of food processing on its antioxidant capacity (8). However, studies focusing on its potential neuroprotective properties remain limited. In this context, the anticholinesterase activities of hexane, ethylacetate, and methanol extracts of *C. lutescens* were systematically evaluated, aiming to provide deeper insights into the possible involvement of mushrooms in the management of neurodegenerative disorders. Such findings may contribute to a broader understanding of the therapeutic potential of *C. lutescens* and highlight its relevance as a source of bioactive compounds in drug discovery research.

Methods

Mushroom Sample Collection and Preparation

Fresh fruit bodies used in this study were collected in January 2024 from Yalova province (Armutlu, Türkiye). A reference sample was deposited with the Department of Medical Biology, Faculty of Medicine, Yalova University accession number SSE24-48, and is available for future reference. The samples identified by Dr. Selime Semra Erol using classical macroscopic and microscopic methods according to the available literature. Specimens identified as *C. lutescens* (Pers.) Fr. 1821 by classical taxonomy were confirmed by molecular taxonomy. The combined morphological and molecular evidence strongly supports the identification of the Turkish isolate as *C. lutescens*. Morphological features such as the funnel-shaped basidiomata, hollow stipe, and orange hymenophore folds are consistent with previous descriptions of the species (9,10). The ITS1-5.8S-ITS2 sequence of the Yalova isolate showed a 98-100% identity with *C. lutescens* voucher A5 from Tunisia (GenBank Accession No. PP533059.1), confirming its taxonomic placement within the *Hydnaceae* (Table 1).

The collected mushrooms were shade-dried at room temperature to prevent thermal degradation of bioactive compounds and then ground into a fine powder using an industrial-scale grinder. The powdered material was stored in airtight containers at 4 °C until further extraction and analytical procedures.

Extraction Process

The dried *C. lutescens* sample (24.57 g) was macerated at room temperature with hexane, ethylacetate, and methanol, successively (Figure 1). The extracts were filtered, and solvents were evaporated under reduced pressure once in every other day until the mushroom material is completely consumed. The maceration step afforded 3 extracts: namely hexane, ethylacetate, and methanol extracts.

Table 1. Comparative table of ITS sequences

Sample	Accession no	Region	Sequence length (bp)	% Identity	Origin
Yalova isolate *(Cantharellus lutescens)*	Pending	ITS1-5.8S-ITS2	507	98-100%	Yalova, Türkiye
Voucher A5 *(Cantharellus lutescens)*	PP533059.1	ITS1-5.8S-ITS2	665	98-100%	Tunisia

Anticholinesterase Activity

To assess the acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitory activities of *C. lutescens*, Ellman method (11) was followed with slight modifications (12). A reaction mixture was prepared by combining 150 µL of 100 mM sodium phosphate buffer (pH 8.0), 10 µL of the test sample (dissolved in ethanol at varying concentrations), and 20 µL of AChE (5.32×10^{-3} U) or BChE (6.85×10^{-3} U) solution, followed by incubation for 15 min at 25 °C. Subsequently, 10 µL of 0.5 mM DTNB solution were added. The reaction was initiated by adding 10 µL of acetylcholine iodide (0.71 mM) or butyrylthiocholine chloride (0.2 mM). The hydrolysis of these substrates was monitored spectrophotometrically at 412 nm by detecting the formation of the yellow 5-thio-2-nitrobenzoate anion, which results from the reaction between DTNB and the thiocholine released during enzymatic hydrolysis of acetylcholine iodide or butyrylthiocholine chloride. Measurements were performed using a 96-well microplate reader. Galantamine is used as the standard drug. The inhibitory activity was expressed as inhibitory concentration (IC_{50}) values, calculated from the concentration-response curve plotting the percentage of enzyme inhibition against sample concentration.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics. The half maximal IC_{50} values obtained from each extract were expressed as mean ± standard deviation (SD) of three independent experiments. Prior to parametric analysis, data were log-transformed ($logIC_{50}$) to improve normality and homogeneity of variance.

The Shapiro-Wilk test was used to assess the normal distribution of the data, and Levene's test was applied to verify the equality of variances. Since the assumptions for normality and homogeneity were met ($p>0.05$), a one-way analysis of variance was conducted to determine whether there were statistically significant differences in IC_{50} values among the extracts. Post-hoc pairwise comparisons were performed using Tukey's honest significant difference and Games-Howell tests to identify specific group differences. The significance level of $p<0.05$ was considered statistically significant.

Ethics Committee Approval

This study does not involve human participants, animal experiments, or private or sensitive data collection. Therefore, ethical approval was not needed. This study does not involve human participants, animal experiments, or private or sensitive data collection. Therefore, informed consent was not needed.

Results

The % AChE inhibition values for hexane, ethyl acetate, and methanol extracts of *C. lutescens* at different concentrations are presented in Table 2 (Figure 2) (separated figures in Supplementary Figure S1-S4). When the AChE inhibitory

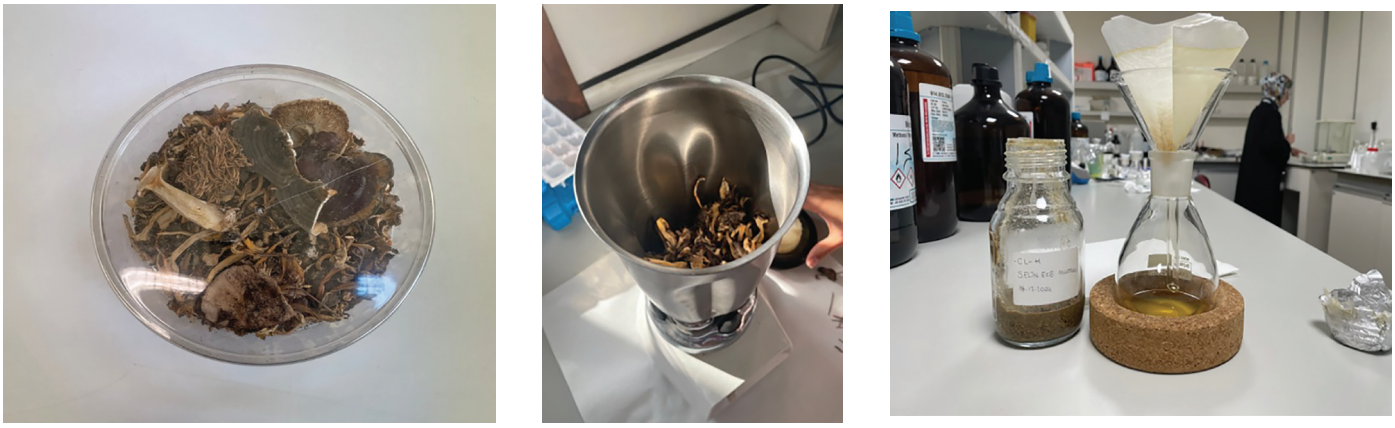

Figure 1. Extraction process

Table 2. The acetylcholinesterase inhibitory activity (%) of *Cantharellus lutescens* extracts

Extracts	Concentration (µg/mL)[a]				IC_{50}
	100	200	400	800	µg/mL
CLH (hexane extract)	15.21±0.84	24.00±1.73	30.33±1.53	48.07±0.51	824.56±10.75
CLE (EtOAc extract)	5.39±0.88	8.79±1.55	15.20±0.20	19.46±1.27	2265.72±15.93
CLM (methanol extract)	NA	NA	1.84±0.12	7.20±1.15	1052.86±15.26
Galantamine[b]	68.36±1.10	74.38±0.65	78.59±0.47	80.40±0.9	5.01±0.01

[a]: All results ± standard deviation (three replicate studies), [b]: Galantamine; standard, NA: Not active, IC_{50}: Inhibitory concentration

activity of *C. lutescens* was assessed, all extracts demonstrated a concentration-dependent increase in inhibition as expected. The highest % inhibition among all the extracts was observed for the hexane extract at a concentration of 800 µg/mL (48.07%) which is comparable to the standard drug galantamine (68.36±1.10). While the methanol extract was found to be inactive at 100 and 200 µg/mL concentrations, ethyl acetate extracts showed some activity at all concentrations.

The BChE inhibition values (%) for hexane, ethylacetate, and methanol extracts of *C. lutescens* at different concentrations are shown in Table 3 (Figure 3) (separated figures in Supplementary Figure S5-S7). When the BChE inhibitory activity of *C. lutescens* was assessed, ethyl acetate extract at a concentration of 800 µg/mL exhibited the highest inhibition % value (29.20±0.80) in comparison to the other extracts. Both the hexane and methanol extracts were found to demonstrate show some inhibition, with the methanol extract displaying superior activity at all concentrations.

Discussion

The present study systematically evaluated the AChE and BChE inhibitory activities of *C. lutescens*, contributing to the growing body of literature investigating natural products for AD therapy. Mushrooms are recognized for their diverse bioactive compounds, including polysaccharides from *Armillaria mellea* (13), cordycepin from *Cordyceps militaris* (14), and ganoderic acids A, B, E, and Y from *Ganoderma lucidum* (15), which exhibit neuroprotective, anti-inflammatory, and antioxidant properties. Among these, erinacine A from *Hericium erinaceus* has attracted particular attention due to its neurotrophic activity and is currently undergoing clinical trials (16). In a randomized, double-blind, placebo-controlled pilot study, patients with early-stage AD receiving *Hericium erinaceus* mycelium and erinacine A for 49 weeks exhibited improvements in instrumental activities of daily living, Mini-Mental State Examination scores, and contrast sensitivity compared to controls. These findings underscore the potential of mushroom-derived compounds as multi-target agents, capable of modulating both cognitive function and underlying neuropathology, though further mechanistic studies are warranted.

Within *Cantharellus* species, *C. tubaeformis* has been reported to inhibit AChE, with its water extract showing the highest activity (42.13±0.51%) and its hexane extract demonstrating the

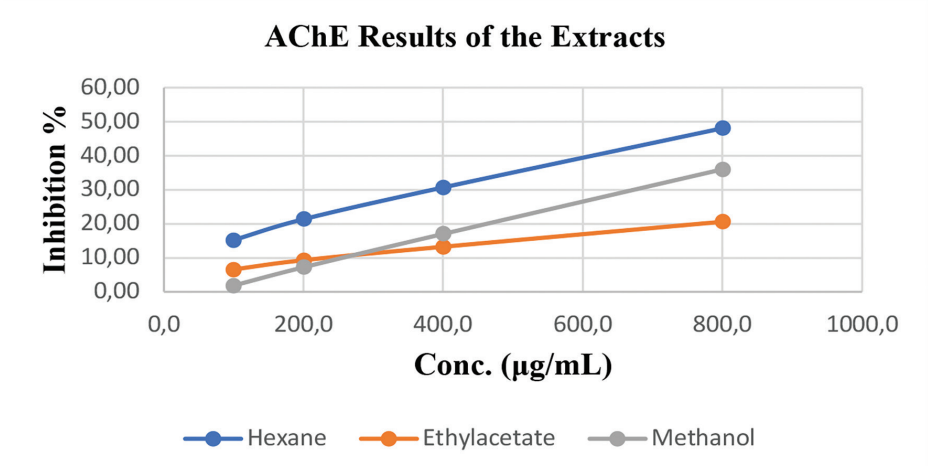

Figure 2. Acetylcholinesterase inhibitory activity of *Cantharellus lutescens* extracts
AChE: Acetylcholinesterase

Table 3. The butyrylcholinesterase inhibitory activity (%) of *Cantharellus lutescens* extracts

Extracts	Concentration (µg/mL)[a]				IC_{50}
	100	200	400	800	µg/mL
CLH (hexane extract)	3.11±0.10	5.01±0.05	7.07±0.05	9.83±0.03	5117.58±0.46
CLE (EtOAc extract)	21.33±1.15	27.40±0.18	28.47±0.10	29.20±0.80	5490.09±6.17
CLM (methanol extract)	8.43±0.08	9.94±0.42	12.81±0.50	17.72±0.93	2999.86±14.30
Galantamine[b]	40.59±2.88	48.73±0.90	65.02±0.44	85.42±0.31	229.45±4.62

[a]: All results ± standard deviation (three replicate studies) [b]: Galantamine; standard, IC_{50}: Inhibitory concentration

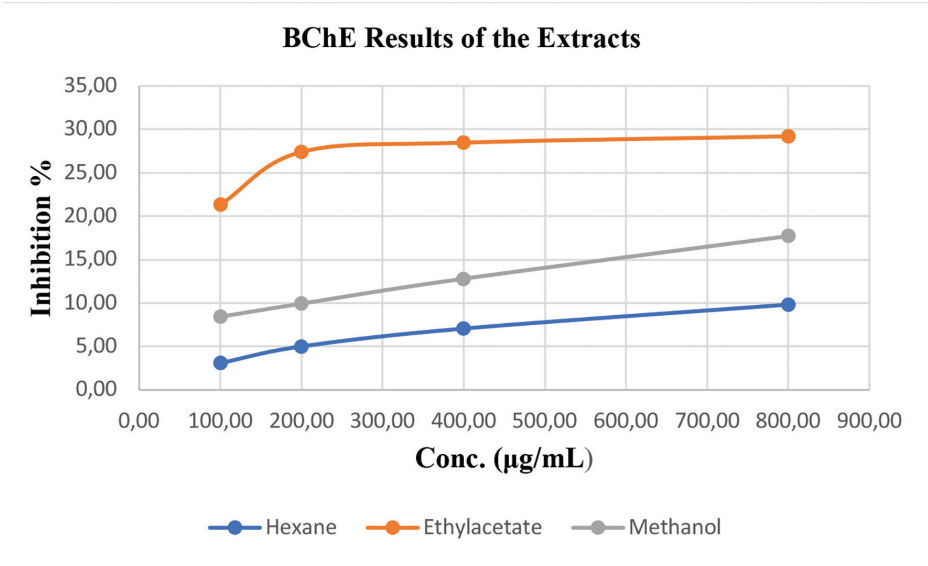

Figure 3. Butyrylcholinesterase inhibitory activity of *Cantharellus lutescens* extracts
BChE: Butyrylcholinesterase

strongest BChE inhibition (29.14±0.04%) (13). Previous studies on *C. lutescens* highlighted its anti-thrombin activity and the influence of industrial processing on antioxidant capacity (17), but its cholinesterase inhibitory potential had not been comprehensively assessed until now.

In the current study, the hexane extract of *C. lutescens* showed 48.07±0.51% AChE inhibition at 800 µg/mL, indicating substantial inhibitory potential, albeit lower than the standard drug galantamine (68.36±1.10% at 100 µg/mL). The ethylacetate extract exhibited 29.20±0.80% BChE inhibition at the same concentration, approaching the activity of galantamine (40.59±2.88% at 100 µg/mL). The methanol extract displayed higher activity than the hexane extract, while other extracts were relatively weak, suggesting that different solvent fractions concentrate distinct bioactive compounds. These observations indicate that *C. lutescens* contains selective cholinesterase inhibitors, supporting its potential as a source of multi-target agents for AD.

Mechanistically, the selective inhibition of AChE and BChE observed in different extracts may reflect the presence of specific terpenoids, phenolics, or fatty acid derivatives, as reported in other *Cantharellus* species. This aligns with the concept that combinatorial bioactivity in mushroom extracts can target multiple pathways relevant to neurodegeneration, including oxidative stress, neuroinflammation, and cholinergic dysfunction. Future studies involving bioassay-guided fractionation, compound isolation, and *in vivo* validation will be essential to identify the active constituents and confirm their therapeutic relevance.

The integration of both morphological and molecular identification of *C. lutescens* strengthens the credibility of the findings and provides a reproducible reference for subsequent studies. Overall, this study highlights the untapped potential of edible and medicinal mushrooms as sources of novel cholinesterase inhibitors, emphasizing the importance of systematic screening, solvent-specific extraction, and mechanistic evaluation in the search for effective natural therapeutics against AD.

Study Limitations

This study, limited to three extracts, offers initial evidence regarding the anti-Alzheimer potential of *C. lutescens*. The isolation and characterization of major bioactive compounds, followed by evaluation of their anticholinesterase activity as well, could provide more targeted and conclusive results.

Conclusion

As a complex disease, multiple mechanisms are thought to play a role in the occurrence and progression of AD. Cholinesterase inhibition is only one mechanism that was the object of this study. Further investigations, including assays on Aβ aggregation inhibition and anti-tau activity, complemented by *in vivo* studies, could provide a more comprehensive understanding of the therapeutic potential of this mushroom, *C. lutescens*. Moreover, as an edible mushroom, conducting cytotoxicity studies on it will be essential to support its potential future use as a therapeutic supplement.

AD is a complex disorder involving multiple pathological mechanisms. Cholinesterase inhibition, which was the focus of this study, represents only one of these pathways. To gain

a more comprehensive understanding of the therapeutic potential of *C. lutescens,* further research should include assays targeting amyloid-β aggregation and tau pathology, supported by *in vivo* studies. In addition, given that it is an edible mushroom, cytotoxicity evaluations will be crucial to confirm its safety and support its prospective use as a therapeutic supplement.

Ethics

Ethics Committee Approval: This study does not involve human participants, animal experiments, or private or sensitive data collection. Therefore, ethical approval was not needed.

Informed Consent: This study does not involve human participants, animal experiments, or private or sensitive data collection. Therefore, informed consent was not needed.

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Authorship Contributions

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

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

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Original Article

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Investigation of the Viscoelastic Properties of Selected Upper Extremity and Cervical Muscles and Movement-based Reaction Time in University Students with Smartphone Addiction

Akıllı Telefon Bağımlılığı Olan Üniversite Öğrencilerinde Seçilmiş Üst Ekstremite ve Servikal Kasların Viskoelastik Özellikleri ile Hareket Temelli Reaksiyon Sürelerinin İncelenmesi

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ABSTRACT

Objective: The aim of this study was to evaluate the relationship between smartphone addiction and the viscoelastic properties (tone, stiffness, elasticity) of selected upper extremity and cervical muscles and movement-based reaction time in university students.

Methods: This cross-sectional study included 216 university students. Participants were divided into addicted and non-addicted groups using the Smartphone Addiction Scale-Short Version (cut-off score: males ≥31, females ≥33). Muscle viscoelastic properties were assessed using the MyotonPRO device, and movement-based reaction time was evaluated via the SWAY application.

Results: Mostly low-level but significant positive correlations were found between muscle viscoelastic properties, screen time, and SWAY average scores. Moderate correlations were

ÖZ

Amaç: Bu çalışmanın amacı, üniversite öğrencilerinde akıllı telefon bağımlılığı ile seçilmiş üst ekstremite ve servikal kasların viskoelastik özellikleri (tonus, sertlik, elastikiyet) ve hareket temelli reaksiyon süresi arasındaki ilişkiyi değerlendirmektir.

Yöntem: Bu kesitsel çalışmaya 216 üniversite öğrencisi dahil edilmiştir. Katılımcılar, Akıllı Telefon Bağımlılığı Ölçeği-Kısa Formu kullanılarak (kesme puanı erkek için ≥31, kadın için ≥33) bağımlı ve bağımlı olmayan gruplara ayrılmıştır. Kas viskoelastik özellikleri MyotonPRO cihazı kullanılarak değerlendirilmiş, hareket temelli reaksiyon süresi ise SWAY uygulaması aracılığıyla değerlendirildi.

Bulgular: Kasların viskoelastik özellikleri, ekran süresi ve SWAY ortalama puanları arasında çoğunlukla düşük düzeyde ancak istatistiksel olarak anlamlı pozitif yönde korelasyon bulundu. Fleksör karpi ulnaris ve ekstansör karpi radialis kaslarının bazı

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ABSTRACT

observed between some parameters of the flexor carpi ulnaris and extensor carpi radialis muscles and both the SWAY average and daily screen time.

Conclusion: Smartphone addiction was associated with changes in selected muscle viscoelastic properties, while only weak associations with movement-based reaction time were observed. These findings suggest that excessive smartphone use may be related to minimal neuromuscular adaptations rather than clinically definitive impairments.

Keywords: Muscle viscoelasticity, reaction time, smartphone addiction, university students

ÖZ

parametreleri ile SWAY ortalama puanı hem de günlük ekran süresi arasında orta düzeyde korelasyonlar gözlendi.

Sonuç: Akıllı telefon bağımlılığı, seçilmiş kasların viskoelastik özelliklerindeki değişikliklerle ilişkili bulunurken, hareket temelli reaksiyon süresi ile yalnızca zayıf düzeyde ilişkiler gözlendi. Bu bulgular, aşırı akıllı telefon kullanımının klinik olarak belirgin bozukluklardan ziyade minimal nöromüsküler adaptasyonlarla ilişkili olabileceğini düşündürmektedir.

Anahtar Kelimeler: Kas viskoelastik özellikleri, reaksiyon süresi, akıllı telefon bağımlılığı, üniversite öğrencileri

Introduction

Smartphone use has increased rapidly worldwide over the past decade, driven by continuous technological advancements. The widespread adoption of smartphones has extended across both high-income and low- and middle-income countries, reflecting the growing accessibility and integration of mobile technologies into everyday life (1,2). Especially among young individuals, smartphones have become an integral part of daily life (3). Browsing the internet, social media applications, mobile games, and high-resolution screen features encourage prolonged usage of these devices, potentially leading to addiction-level usage (4).

Among young adults such as university students, the increasing frequency and duration of smartphone use has been associated with musculoskeletal pain and discomfort (4). Factors such as maintaining the same posture for extended periods, performing repetitive movements, and focusing on screens positioned below eye level contribute to increased mechanical load on the upper extremity and cervical musculoskeletal system (5). Continuous use of shoulder, forearm, and wrist muscles in this manner may increase the risk of musculoskeletal disorders and functional impairment of the upper extremity (6,7). Sharan et al. (7) reported that prolonged device usage was associated with musculoskeletal disorders in the upper extremity. Ha and Sung (8) reported that temporary forward head posture reduced cervical proprioceptive function. Son et al. (9) found that smartphone use exceeding 15 minutes negatively affected the viscoelastic properties of the masseter and digastric muscles.

These types of chronic musculoskeletal loadings can eventually lead to decreased movement efficiency and reduced functional capacity (10). Furthermore, movement-based reaction time, defined as the individual's response time to environmental stimuli, is closely related to neuromuscular coordination (11). Gada and Dhasal (12), in a study involving individuals aged 18-25, found no significant correlation between difference between smartphone screen time and reaction time. However, Jiménez-García et al. (13) found that muscle strength and physical performance were significantly associated with reaction time in older adults. Impaired sensorimotor control may adversely affect postural stability and movement performance (14).

Although previous studies have separately investigated the musculoskeletal effects of smartphone use (15,16) or its relationship with reaction time (11-13), no previous study has simultaneously examined the association between smartphone addiction, upper extremity muscle viscoelastic properties, and movement-based reaction time. In light of this information, the aim of this study is to evaluate the viscoelastic properties (tone, stiffness, elasticity) of selected upper extremity and cervical muscles and movement-based reaction times in university students with smartphone addiction, and to investigate the relationship between these variables. We hypothesized that higher levels of smartphone addiction would be associated with increased muscle tone and stiffness, decreased muscle elasticity, and prolonged movement-based reaction time.

Methods

This cross-sectional study was conducted in the practice laboratory of the Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, SANKO University. The study sample consisted of volunteer students from the Faculty of Health Sciences at SANKO University. Prior to the start of the study, ethical approval was obtained from the Non-Interventional Ethics Committee of SANKO University in accordance with the principles of the Declaration of Helsinki (decision no: 2025/03, date: 12.03.2025).

The study procedures were explained in detail to the participants, and written informed consent was obtained from all individuals. The entire research process adhered to the principles of the Strengthening the Reporting of Observational Studies in Epidemiology guideline. Sociodemographic data of the participants were collected using a personal information form developed by the researchers. Dominant upper extremity was determined

based on participants' self-report (17). Daily and weekly screen time was recorded by checking the "settings" section of the participants' smartphones. In addition, the screen sizes of the phones were measured diagonally from the bottom-left to the top-right corner using a measuring tape, and results were calculated in both centimeters and inches. Participants' habitual physical activity level, ergonomic posture during smartphone use, and habitual sitting posture were not quantitatively assessed and therefore were not included in the statistical analyses. Inclusion criteria were: being between 18-35 years old, having used a touchscreen smartphone for at least 1 year, and using the smartphone for more than 60 minutes daily (18). Exclusion criteria included: having a neurological, rheumatological, or musculoskeletal disease or cognitive impairment; having had an upper extremity injury or surgery within the past 6 months; a body mass index >35 kg/m²; participation in an upper extremity exercise program within the past 6 months; presence of joint contracture in the upper extremity; inability to comply with the assessment protocol; incomplete participation; or refusal to participate in the study. To determine the level of smartphone addiction, the Smartphone Addiction Scale-Short Version (SAS-SV) was used. According to this scale, the cut-off score was ≥31 for males and ≥33 for females. Based on the results, participants were divided into two groups: addicted and non-addicted (19). The viscoelastic properties (tone, stiffness, elasticity) of the upper extremity muscles were assessed using the MyotonPRO device (Myoton Ltd., Tallinn, Estonia) (20). Movement-based reaction times were measured using the validated SWAY mobile application (21). The SWAY Cognitive Assessment application has been shown to provide valid and reliable movement-based reaction time measurements (22). VanRavenhorst-Bell et al. (22) demonstrated that SWAY reaction time metrics were comparable with the FDA-approved ImPACT Quick Test and operated reliably across different mobile devices and operating systems. The authors further reported that the motion-based, triaxial accelerometer system used by SWAY minimizes device latency and allows highly sensitive detection of sensorimotor responses, supporting its use for evaluating reaction time in research settings (22). During the assessment, participants were tested in a standardized upright standing position, holding the smartphone with both hands at chest level. Reaction time was evaluated using visually presented stimuli only, and participants were instructed to respond to the appearance of the stimulus on the screen as quickly as possible (21,22). To ensure data confidentiality, each participant was assigned a code number. Data were organized in Microsoft Excel and were accessible only to members of the research team.

SAS-SV

The level of smartphone addiction was assessed using the SAS-SV, developed by Kwon et al. (19) and adapted into Turkish by Noyan et al. (23). The scale consists of 10 items scored on a six-point Likert scale. Higher scores indicate an increased risk of smartphone addiction. Necessary permissions for the use of the scale were obtained Based on gender-specific cut-off scores, participants were divided into two groups: "addicted" and "non-addicted" (19,23).

Assessment of Muscle Viscoelastic Properties

The viscoelastic properties (tone, stiffness, and elasticity) of selected upper extremity and cervical muscles were evaluated using the MyotonPRO device (Myoton Ltd., Tallinn, Estonia), a non-invasive and digital measurement tool (20). This device enables objective evaluation of the mechanical properties of muscles, tendons, ligaments, skin, and other superficial soft tissues (20). Previous studies have demonstrated high intra-rater, inter-rater, and test-retest reliability for MyotonPRO measurements. A recent systematic review reported good to excellent reliability across different muscles and anatomical regions, with intraclass correlation coefficient (ICC) values ranging from -0.15 to 0.99 (24). In addition, Valenti et al. (25) showed good to excellent intra-rater (ICC: 0.88-0.91) and inter-rater reliability (ICC: 0.84-0.96) for lumbar erector spinae stiffness measurements using MyotonPRO.

The measurements obtained from the MyotonPRO were based on the following three core parameters: muscle tone (Hz); indicates the basic tension level of the muscle at rest. Stiffness (N/m); reflects the biomechanical resistance of the tissue to external force. Elasticity; refers to the speed at which tissue returns to its original shape after deformation, measured by the logarithmic decrement of oscillation (26). The following muscles were evaluated bilaterally using the MyotonPRO device: semispinalis capitis, biceps brachii, brachioradialis, extensor digitorum, extensor carpi radialis, flexor carpi radialis, and flexor carpi ulnaris. Measurement sites for all muscles were identified according to previously published anatomical protocols, and the anatomical landmarks and measurement procedures were applied as originally described in these studies (26,27).

All MyotonPRO assessments were performed after a 3-5-minute rest period while participants were seated in a standardized upright position. During the measurements, participants sat comfortably on a chair with the shoulder in a neutral position, the elbow flexed to 90°, the forearm resting on a support, and the wrist maintained in a neutral position to ensure complete muscle relaxation and to minimize involuntary muscle activation. Three consecutive measurements were obtained from each muscle, and the mean value was used for statistical analysis. All measurements were performed by the same experienced physiotherapist while the target muscles remained in a relaxed, passive state. To minimize order effects, both the sequence of muscle assessments and the dominant-non-dominant side measurement order were randomized for each participant. Measurement sites were determined according to previously published anatomical protocols (26-28).

Ethics Committee

This study was approved by the Non-Interventional Ethics Committee of SANKO University as item number 1 on the agenda of meeting number 2025/03, held on March 12, 2025.

Statistical Analysis

According to the power analysis, assuming α=0.05 and 1-β (power) =0.80, and based on a 4.7-point difference in Smartphone Addiction Scale scores between group 1 (26.9±10.8) and group 2 (31.6±11.3), a minimum of 87 participants per group was required, for a total sample size of 174 university students (29). The sample size was calculated using the NCSS PASS 13 software. In addition, a post-hoc power analysis was conducted using the OpenEpi software (version 3) based on the observed group differences in right brachioradialis muscle tone (15.27±2.21 vs. 16.16±2.39). The achieved statistical power was 81.16%, confirming that the sample size was sufficient to detect meaningful differences in muscle viscoelastic properties (30). Descriptive statistics were presented as mean and standard deviation or median and minimum-maximum values for numerical variables, and frequencies and percentages for categorical variables. The Shapiro-Wilk test was used to assess the normality of numerical variables. Since parametric test assumptions were not met, the Mann-Whitney U test was used to compare two independent groups for numerical variables. The chi-square test was used to compare categorical variables. Relationships between two numerical variables were assessed using Spearman's rank correlation coefficient. A significance level of $p<0.05$ was considered statistically significant. All data were analyzed using IBM SPSS Statistics 23 software (31). Interpretation of Spearman correlation coefficients was as follows (32): 0.00-0.10: very weak or negligible correlation, 0.10-0.39: weak correlation, 0.40-0.69: moderate correlation, 0.70-0.89: strong correlation, 0.90-1.00: very strong correlation. Given the large number of statistical comparisons performed across multiple muscles, parameters (tone, stiffness, elasticity), sides (right/left), and sex-stratified analyses (total, male, female), the risk of type I error inflation was addressed using false discovery rate correction. Specifically, the Benjamini-Hochberg procedure was applied to the p-values obtained from each family of related tests. For each muscle, p-values from the total sample and sex-specific comparisons were adjusted within that muscle, rather than across all tests, in order to preserve anatomical and physiological interpretability while adequately controlling for multiple testing. Adjusted p-values (q-values) <0.05 were considered statistically significant. Statistically significant adjusted p-values are presented in bold in the tables (33,34).

Results

Demographic Characteristics of the Participants

A total of 216 university students were included in the study, of whom 51.9% were classified as smartphone-addicted. There were no statistically significant differences between the smartphone-addicted and non-addicted groups in terms of age, gender distribution, or dominant upper extremity (all $p>0.05$) (Table 1).

Viscoelastic Properties of the Participants' Muscles

Overall, most upper extremity muscle viscoelastic parameters did not differ significantly between the smartphone-addicted and non-addicted groups. Statistically significant between-group differences were limited to muscle tone in selected distal upper extremity muscles, including the brachioradialis, extensor digitorum, biceps brachii, flexor carpi radialis, and extensor carpi radialis. In addition, left-side muscle stiffness of the extensor carpi radialis was significantly higher in the smartphone-addicted group. These findings were more pronounced among female participants. Detailed numerical results are presented in (Table 1; Supplementary Table 1).

The Relationship Between the Viscoelastic Properties of Participants' Muscles and Movement-based Reaction Times

Spearman correlation analysis revealed that most associations between screen time, viscoelastic muscle properties, and movement-based reaction time were statistically significant but weak in magnitude. In addition, weak to moderate correlations were observed between movement-based reaction time and upper extremity muscle tone and stiffness; however, these associations were modest in magnitude Table 2; Supplementary Table 2 A-C.

Discussion

This study aimed to reveal the relationship between smartphone addiction, muscle viscoelastic properties, and movement-based reaction time in university students. Smartphone addiction was associated with selective differences in muscle tone in specific upper extremity muscles; however, given the cross-sectional design of the study, these findings should be interpreted as associative rather than causal.

These findings suggest that, even in young adults, smartphone use may be associated with early and subtle changes in muscle biomechanics. However, because of the cross-sectional design, these observations should be interpreted as preliminary associations rather than clinically definitive effects.

Table 1. Comparison of variables according to smartphone addiction in all participants

Variables			Non-smartphone-addicted (n=104)			Smartphone-addicted (n=112)			Total	Male	Female
			Total mean ± SD (min-max)	Male mean ± SD (min-max)	Female mean ± SD (min-max)	Total mean ± SD (min-max)	Male mean ± SD (min-max)	Female mean ± SD (min-max)	q	q	q
Age			20.4±1.5 (18.0-24.0)	20.7±1.5 (18.0-23.0)	20.3±1.5 (18.0-24.0)	20.5±1.6 (18.0-29.0)	20.5±1.4 (18.0-25.0)	20.5±1.7 (18.0-29.0)	0.704	0.483	0.420
Body mass index (kg/m²)			23.11±3.82 (17.57-34.19)	25.12±4.24 (17.87-34.19)	21.99±2.90 (17.57-32.14)	23.52±3.75 (17.69-34.19)	25.48±3.84 (19.38-34.19)	22.48±2.75 (17.69-33.20)	0.804	0.544	0.552
Daily screen time (hours)			4.7±2.0 (1.0-12.0)	4.8±2.6 (1.0-12.0)	4.7±1.7 (1.0-10.0)	6.0±3.1 (1.0-20.0)	7.1±4.0 (1.5-20.0)	5.4±2.3 (1.0-17.0)	**0.001**	**0.010**	**0.035**
Weekly screen time (hours)			30.7±14.0 (3.0-80.0)	33.3±17.3 (3.0-80.0)	29.6±12.4 (5.0-58.0)	34.7±17.5 (3.0-140.0)	38.1±22.3 (10.0-140.0)	32.7±13.7 (3.0-60.0)	0.70	0.485	0.098
Smartphone screen size (inches)			6.65±0.32 (5.91-7.87)	6.70±0.21 (6.30-7.09)	6.64±0.36 (5.91-7.87)	6.65±0.30 (5.91-7.48)	6.58±0.31 (5.91-7.09)	6.69±0.28 (5.91-7.48)	0.628	0.062	0.475
Mean movement-based reaction time (SWAY)			267.17±37.40 (183.6-418.4)	264.71±35.90 (199.4-371.6)	268.16±38.18 (183.6-418.4)	268.42±41.22 (184.4-384)	281.99±43.72 (184.4-380)	260.28±37.66 (197.6-384.0)	0.883	0.068	0.183
SC	**Tone**	**Right**	14.4±1.7 (11.3-20.0)	14.2±1.5 (11.6-16.8)	14.4±1.7 (11.3-20.0)	14.1±1.1 (12.3-19.2)	14.3±0.9 (12.3-15.9)	13.9±1.2 (12.3-19.2)	0.397	0.736	0.138
		Left	15.2±2.0 (12.0-20.7)	15.3±1.7 (12.0-18.2)	15.2±2.2 (12.3-20.7)	15.7±1.9 (11.2-20.2)	15.9±1.7 (11.2-20.2)	15.6±2.0 (12.5-20.2)	0.037	0.073	0.220
	Stiffness	**Right**	225.2±44.8 (139-390)	219.3±35.5 (139-272)	227.5±48.1 (157-390)	215.8±38.7 (152-485)	224.6±28.1 (157-312)	210.6±43.2 (152-485)	0.090	0.702	0.044
		Left	244.9±54.3 (144-432)	248.9±42.0 (148-351)	243.3±58.7 (144-432)	251.9±49.3 (157-399)	256.9±45.7 (167-361)	248.9±51.4 (157-399)	0.225	0.482	0.392
	Elasticity	**Right**	1.11±0.13 (0.82-1.51)	1.09±0.14 (0.85-1.37)	1.12±0.12 (0.82-1.51)	1.10±0.14 (0.85-1.99)	1.14±0.17 (0.85-1.99)	1.07±0.12 (0.89-1.54)	0.213	0.390	0.014
		Left	1.09±0.13 (0.81-1.77)	1.06±0.09 (0.88-1.30)	1.11±0.15 (0.81-1.77)	1.07±0.18 (0.77-2.06)	1.09±0.17 (0.92-1.57)	1.06±0.19 (0.77-2.06)	0.12	0.868	0.003
BR	**Tone**	**Right**	14.7±1.7 (11.4-18.7)	14.7±1.3 (12.5-18.7)	14.7±1.9 (11.4-18.6)	15.3±1.5 (11.3-19.3)	14.7±0.8 (13.1-16.2)	15.7±1.7 (11.3-19.3)	**0.003**	0.267	0.002
		Left	15.21±2.21 (11.4-22.7)	16.28±2.23 (13.1-22.7)	14.78±2.06 (11.4-22.6)	16.04±1.52 (11.6-19)	16.51±1.33 (13.7-19)	15.75±1.57 (11.6-18.8)	**0.001**	0.150	**0.001**
	Stiffness	**Right**	243.5±52.3 (137-379)	244.6±40.9 (181-379)	243.1±56.5 (137-379)	256.7±43.5 (142-350)	248.4±32.3 (172-350)	261.7±48.6 (142-337)	0.015	0.202	0.028
		Left	257.0±63.2 (132-485)	282.3±59.5 (170-485)	246.8±62.2 (132-480)	273.9±41.0 (138-350)	285.4±42.7 (200-324)	267.0±38.7 (138-350)	**0.001**	0.373	0.002
	Elasticity	**Right**	0.93±0.12 (0.63-1.31)	0.92±0.11 (0.63-1.12)	0.94±0.12 (0.66-1.31)	0.93±0.10 (0.72-1.29)	0.94±0.08 (0.73-1.10)	0.92±0.12 (0.72-1.29)	0.809	0.344	0.382
		Left	1.00±0.20 (0.70-1.67)	0.96±0.15 (0.78-1.67)	1.02±0.21 (0.70-1.67)	0.97±0.15 (0.68-1.63)	0.97±0.12 (0.78-1.40)	0.97±0.16 (0.68-1.63)	0.674	0.744	0.593

Table 1. continued

Variables			Non-smartphone-addicted (n=104)			Smartphone-addicted (n=112)			Total	Male	Female
			Total mean ± SD (min-max)	Male mean ± SD (min-max)	Female mean ± SD (min-max)	Total mean ± SD (min-max)	Male mean ± SD (min-max)	Female mean ± SD (min-max)	q	q	q
ED	Tone	Right	19.89±3.34 (12.6-27.2)	20.37±2.91 (13.7-25.4)	19.69±3.50 (12.6-27.2)	20.83±3.51 (12.9-27.9)	21.29±2.41 (15.70-25.80)	20.56±4.01 (12.90-27.90)	**0.040**	0.184	0.183
		Left	19.2±3.5 (12.7-27.6)	19.7±2.8 (12.7-25.0)	19.0±3.7 (13.5-27.6)	22.9±1.2 (12.9-28.1)	20.6±2.1 (13.2-24.0)	24.3±6.7 (12.9-26.1)	**0.001**	0.190	0.004
	Stiffness	Right	467.5±155.6 (204-779)	464.8±126.44 (204-662)	468.6±166.7 (219-779)	494.8±157.3 (199-739)	510.4±111.2 (264-695)	485.4±179.5 (199-739)	0.158	0.132	0.503
		Left	445.78±155.9 (222-772)	482.77±142.15 (231-689)	430.78±159.67 (222-772)	510.91±171.87 (193-781)	536.98±110.03 (224-624)	495.27±199.16 (182.1-781.0)	0.002	0.087	0.036
	Elasticity	Right	1.15±0.19 (0.80-1.94)	1.17±0.21 (0.81-1.55)	1.14±0.19 (0.80-1.94)	1.15±0.19 (0.80-1.57)	1.26±0.22 (0.88-1.57)	1.09±0.14 (0.80-1.50)	0.766	0.075	0.145
		Left	1.10±0.20 (0.62-1.70)	1.10±0.20 (0.62-1.38)	1.10±0.21 (0.70-1.70)	1.27±1.71 (0.70-1.91)	1.17±0.15 (0.72-1.37)	1.33 ±0.16 (0.70-1.91	0.423	0.229	0.669

SD: Standard deviation, SC: Semispinalis capitis, BR: Brachioradialis, ED: Extensor digitorum, kg: Kilogram, m: Meter, cm: Centimeter, Bold values indicate statistical significance after Benjamini-Hochberg false discovery rate correction (q<0.05)

Viscoelastic Properties of Muscles in Participants

Although no previous study has directly examined the effects of smartphone addiction on the viscoelastic properties of muscles, several studies have investigated the musculoskeletal consequences of prolonged smartphone use (5-7). These studies have shown that increased screen time, prolonged static postures may contribute to musculoskeletal symptoms, postural deviations and neck disability (5,6).

In this context, significant differences were limited to muscle tone in the brachioradialis, extensor digitorum,

biceps brachii, flexor carpi radialis, and extensor carpi radialis muscles. These selective increases in muscle tone may reflect adaptive neuromuscular responses to sustained gripping, repetitive finger movements, and prolonged wrist flexion postures commonly adopted during smartphone use. Such changes may contribute to impaired muscle function and increase the risk of musculoskeletal discomfort, fatigue, and postural alterations over time (6,7).

The fact that a greater number of muscle groups and parameters showed statistical significance among female participants suggests that neuromuscular responses to smartphone use may differ by gender. Testosterone has been shown to be positively associated with muscle strength and mass, and its lower circulating levels in females may contribute to altered connective tissue composition and increased susceptibility to mechanical loading (35). In addition to hormonal influences, postural and ergonomic factors may play an important role. Previous studies have indicated that women tend to adopt greater cervical and wrist flexion angles and more sustained static postures during smartphone use, resulting in higher cumulative mechanical stress on upper extremity muscles (36). Differences in postural habits, device handling, and prolonged unilateral use patterns may further exacerbate this vulnerability. Together, these hormonal, biomechanical, and ergonomic factors may partially explain why viscoelastic muscle alterations were more pronounced in female participants in the present study (35,36).

Furthermore, muscle viscoelastic properties are influenced by physiological factors such as muscle fatigue and the level of muscle activation (37). In addition to individual differences in muscle structure, it has been reported that whether a muscle is evaluated in a horizontal or vertical position can influence measurement outcomes (38). Therefore, in this study, all assessments were performed in a standardized seated position and with muscles in a passive state to ensure measurement standardization. Differences observed between right and left side muscles may also be attributed to dominant limb discrepancies (20).

Table 2. The relationship between muscle viscoelastic properties and movement-based reaction time

				Total (n=216)						Non-smartphone-addicted (n=104)						Smartphone-addicted (n=112)					
				SWAY	Age	BMI (kg/m²)	Daily screen time (hours)	Weekly screen time (hours)	Smartphone screen size (inches)	SWAY	Age	BMI (kg/m²)	Daily screen time (hours)	Weekly screen time (hours)	Smartphone screen size (inches)	SWAY	Age	BMI (kg/m²)	Daily screen time (hours)	Weekly screen time (hours)	Smartphone screen size (inches)
SWAY			r	1	-0.02	0.09	0.28*	0.03	0.16	1	0.12	0.09	0.31*	0.21*	-0.03	1	-0.05	0.05	0.10	-0.04	-0.01
			p		0.87	0.43	0.01	0.791	0.17	.	0.22	0.32	0.00	0.03	0.75	.	0.54	0.55	0.25	0.65	0.86
Age			r	-0.02	1	0.27*	0.14	0.24*	-0.06	0.12	1	0.347*	0.02	0.03	-0.15	-0.05	1	-0.02	0.10	0.09	-0.06
			p	0.87		0.01	0.22	0.03	0.60	0.22	.	0.0	0.83	0.76	0.10	0.54	.	0.80	0.25	0.30	0.47
BMI (kg/m²)			r	0.09	0.27*	1	0.15	0.03	0.07	0.09	0.34*	1	0.00	0.04	0.14	0.05	-0.02	1	0.11	-0.01	-0.06
			p	0.43	0.01		0.20	0.74	0.54	0.32	0.00	.	0.98	0.64	0.14	0.55	0.80	.	0.21	0.86	0.50
Daily screen time (hours)			r	0.28*	0.14	0.15	1	0.71*	-0.04	0.31*	0.02	0.00	1	0.86*	-0.01	0.10	0.10	0.11	1	0.69*	-0.06
			p	0.01	0.22	0.20		0.0	0.68	0.00	0.83	0.98	.	0.0	0.91	0.25	0.25	0.21	.	0	0.47
Weekly screen time (hours)			r	0.03	0.24*	0.03	0.71*	1	0.09	0.21*	0.03	0.04	0.86*	1	0.07	-0.04	0.09	-0.01	0.69*	1	-0.07
			p	0.79	0.03	0.74	0.0		0.44	0.03	0.76	0.64	0.0	.	0.45	0.65	0.30	0.86	0.0	.	0.44
Smartphone screen size (inches)			r	0.16	-0.06	0.07	-0.04	0.09	1	-0.03	-0.15	0.14	-0.01	0.07	1	-0.01	-0.06	-0.06	-0.06	-0.07	1
			p	0.17	0.60	0.54	0.68	0.44	-	0.75	0.10	0.14	0.91	0.45	.	0.86	0.47	0.50	0.47	0.44	.
SC	**Tone**	**Right**	r	0.22	0.13	0.02	0.12	-0.00	0.03	-0.02	0.06	0.07	0.09	0.03	0.10	0.03	0.11	0.18	0.04	-0.14	-0.09
			p	0.05	0.26	0.85	0.28	0.94	0.77	0.83	0.50	0.46	0.32	0.76	0.26	0.68	0.24	0.05	0.66	0.13	0.32
		Left	r	0.27*	0.03	0.19	0.12	0.00	0.00	0.17	0.06	0.02	0.17	0.23*	0.19*	0.27*	0.11	0.12	-0.07	-0.02	0.01
			p	0.02	0.74	0.10	0.28	0.95	0.97	0.07	0.48	0.80	0.07	0.01	0.04	0.00	0.22	0.17	0.43	0.83	0.84
	Stiffness	**Right**	r	0.31*	0.11	0.06	0.15	0.05	0.04	-0.02	0.05	0.07	0.10	0.03	0.06	0.15	-0.02	0.28*	0.08	-0.11	-0.06
			p	0.00	0.32	0.59	0.18	0.64	0.70	0.77	0.59	0.43	0.27	0.69	0.53	0.09	0.82	0.00	0.38	0.22	0.52
		Left	r	0.12	0.00	0.17	0.01	-0.07	-0.00	0.18	-0.00	-0.00	0.11	0.12	0.12	0.17	0.16	0.08	-0.10	-0.07	0.02
			p	0.31	0.96	0.13	0.91	0.56	0.96	0.06	0.98	0.95	0.26	0.21	0.21	0.06	0.07	0.38	0.28	0.41	0.82
	Elasticity	**Right**	r	0.27*	0.00	0.15	0.06	-0.05	0.05	0.10	0.10	0.24*	0.06	-0.03	0.07	0.25*	0.13	0.26*	0.06	0.01	-0.08
			p	0.01	0.94	0.20	0.58	0.65	0.66	0.30	0.26	0.01	0.49	0.75	0.45	0.00	0.14	0.00	0.52	0.91	0.37
		Left	r	-0.15	0.01	0.02	-0.17	-0.16	-0.00	-0.08	0.03	0.00	-0.11	-0.20*	-0.04	-0.00	0.09	0.12	-0.06	-0.13	-0.04
			p	0.20	0.91	0.85	0.14	0.17	0.93	0.41	0.76	0.92	0.25	0.04	0.66	0.93	0.34	0.17	0.47	0.15	0.61
BR	**Tone**	**Right**	r	-0.16	-0.02	-0.07	-0.22	-0.31*	0.04	0.08	0.04	-0.05	-0.03	0.03	-0.07	-0.07	0.23*	-0.26*	-0.20*	-0.11	0.17
			p	0.15	0.83	0.53	0.06	0.00	0.71	0.39	0.66	0.60	0.73	0.72	0.46	0.42	0.01	0.00	0.03	0.24	0.06
		Left	r	0.38*	0.15	0.07	0.25*	0.08	0.26*	0.19*	0.26*	0.17	0.22*	0.28*	-0.05	0.35*	0.03	0.07	0.13	0.07	0.18*
			p	0.00	0.20	0.55	0.03	0.50	0.02	0.04	0.00	0.08	0.02	0.00	0.60	0.0	0.71	0.43	0.15	0.43	0.04

BMI: Body mass index, kg: Kilogram, m: Meter, cm: Centimeter, SC: Semispinalis capitis, BR: Brachioradialis, BB: Biceps brachii, FDS: Flexor digitorum superficialis, FCU: Flexor carpi ulnaris, FCR: Flexor carpi radialis, ECR: Extansor carpi radialis, *: p<0.05 indicates statistically significant results

In conclusion, these findings indicate early and subtle neuromuscular adaptations rather than clinically definitive impairments. The findings suggest that smartphone use may be associated with subtle alterations in the neuromuscular system, which may represent early biomechanical adaptations. This highlights the need for the development of preventive physiotherapy strategies and the management of smartphone use duration, especially in young populations. The results should be supported by more advanced biochemical and neurophysiological evaluations and confirmed by longitudinal studies involving different age groups. From a preventive perspective, even subtle increases in muscle tone during early adulthood may, if sustained over time, contribute to cumulative neuromuscular loading, reduced movement efficiency, and impaired motor responsiveness in later years. Early identification of these changes provides an opportunity for physiotherapists to implement targeted interventions such as postural education, activity pacing, and exercise-based strategies to mitigate the long-term neuromuscular consequences of intensive smartphone use (39).

Relationship Between Muscle Viscoelastic Properties and Movement-based Reaction Times

This study aimed to shed light on the effects of digital habits on the neuromuscular system by examining the relationship between smartphone use duration, muscle viscoelastic properties, and movement-based reaction time. The findings revealed that muscle tone, stiffness, and elasticity parameters were significantly, though mostly weakly, associated with variables such as daily screen exposure, screen size, and age. This suggests the presence of early biomechanical changes that may not yet manifest as clinical symptoms. In particular, the correlations observed between SWAY data and certain muscle parameters (e.g., FCU and ECR), although mostly weak in magnitude, may indicate early trends in neurophysiological adaptations that warrant further investigation. Although several correlations reached statistical significance, most of the correlation coefficients were weak ($r<0.40$). This indicates that, while smartphone use and muscle viscoelastic parameters are related to movement-based reaction time, these associations are modest and other unmeasured factors are also likely to contribute to reaction time performance.

In the literature, the impact of technology interaction on postural control has received increasing attention in recent years. Numerous studies have reported that smartphone use, being a dual-task activity, may impair postural stability, motor coordination, and movement-based reaction time by dividing attention (40-42). These findings are consistent with the correlations observed in our study and suggest that digital habits may significantly affect muscle function and motor control capacity, especially in young adults.

Considering the participants' age range and screen time criteria, these findings suggest a possible association between intensive smartphone use and altered neuromuscular responses. Although the literature has not consistently shown a direct significant relationship between screen time and reaction time (12), this may be due to the limitations of measuring acute effects. Previous studies in older adults have reported that higher levels of smartphone addiction were associated with shorter reaction times (42). However, such conflicting findings suggest that neuromuscular adaptations may vary based on age, usage habits, and assessment methodologies.

Changes in muscle tone, stiffness, and elasticity are known to influence motor unit activation and the muscle's ability to respond rapidly (43,44). Reaction time is a function not only of cognitive processes but also of the mechanical properties of muscles (45). Therefore, deviations in viscoelastic parameters may influence movement initiation and affect muscle performance in time-sensitive motor tasks. This should be carefully considered in individuals exhibiting increased muscle rigidity due to prolonged screen exposure.

In this study, moderate correlations observed between reaction time and elasticity/stiffness parameters of distal muscle groups such as the FCU and ECR suggest a potential contribution of upper extremity muscle structure in reflexive motor responses. Altered muscle mechanical properties may adversely affect performance during tasks requiring rapid motor responses and efficient sensorimotor control (46). These findings suggest that muscle viscoelastic properties may contribute to movement-based reaction time performance not only for force generation and postural support but also for timing-based motor performance.

From a clinical perspective, viscoelastic changes in muscle tissue associated with smartphone use may warrant consideration not only in terms of ergonomics or pain, but also with regard to reaction time, motor acceleration capacity, and postural balance performance; however, the present findings represent preliminary associations rather than strong clinical effects. In this context, the potential effects of a technology-based lifestyle on the muscular and nervous systems in young individuals should be assessed at an early stage and supported with appropriate physiotherapy strategies.

Study Limitations

Several limitations of this study may affect the generalizability of the findings. Firstly, the sample consisted solely of university students, which limits the applicability of the results to individuals from different age groups or occupational backgrounds. In addition, the use of a cross-sectional design restricts the ability to establish cause-and-effect relationships and only allows for correlational interpretations.

Furthermore, participants' habitual physical activity levels, posture habits, and ergonomic behaviors during smartphone use were not assessed. These factors are

known to influence both muscle viscoelastic properties and reaction time and may therefore have acted as potential confounders in the present study. Another limitation of this study is the absence of intra-rater or test-retest reliability analysis within the current sample. Although MyotonPRO has been shown to provide good to excellent reliability in previous studies, the lack of device-specific reliability testing in our cohort should be considered when interpreting the results.

Reaction time was assessed solely based on the SWAY average, and cognitive and environmental variables that may influence this parameter were not controlled. Similarly, muscle viscoelastic properties were evaluated only in selected muscle groups, which may not provide a comprehensive picture of overall muscle function.

Future studies should consider employing longitudinal research designs involving different age groups to track the effects of smartphone use on the neuromuscular system over time. Moreover, assessments should not be limited to tone, stiffness, and elasticity; a broader range of muscle performance parameters such as strength, endurance, and motor control should also be evaluated. Reaction time, on the other hand, should be examined in a multidimensional manner, incorporating both cognitive and physical components.

From a preventive perspective, if confirmed by longitudinal studies, alterations in muscle viscoelastic properties could potentially contribute young individuals to early fatigue during fine motor tasks, reduced hand dexterity, impaired academic performance, and decreased postural control. Over time, these neuromuscular alterations may contribute to the development of chronic neck-upper extremity pain syndromes, reduced movement efficiency, and a higher risk of cumulative trauma disorders. Therefore, prolonged exposure to digital devices in early adulthood should not only be considered a behavioral issue but also a potential risk factor for long-term neuromuscular health.

Conclusion

This study demonstrated that smartphone addiction was associated with selected changes in muscle viscoelastic properties. Weak associations were also observed between certain muscle viscoelastic parameters and movement-based reaction time. Because of the cross-sectional design, these findings should be interpreted as associative rather than causal. Further longitudinal studies are required to clarify whether these biomechanical alterations have clinically meaningful consequences.

Ethics

Ethics Committee Approval: Prior to the start of the study, ethical approval was obtained from the Non-Interventional Ethics Committee of SANKO University in accordance with the principles of the Declaration of Helsinki (decision no: 2025/03, date: 12.03.2025).

Informed Consent: The study procedures were explained in detail to the participants, and written informed consent was obtained from all individuals.

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Footnotes

Authorship Contributions

Concept: E.R., S.G., M.Y., B.H.Ç., İ.B., N.D.T.G., Design: E.R., S.G., M.Y., B.H.Ç., İ.B., N.D.T.G., Data Collection or Processing: E.R., S.G., M.Y., B.H.Ç., İ.B., N.D.T.G., Analysis or Interpretation: E.R., Literature Search: E.R., Writing: E.R., S.G., M.Y., B.H.Ç., İ.B., N.D.T.G.

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Original Article

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The Investigation of the Effects of Psychogenic Factors on Craniocervical Pain and Disability in Academics

Akademisyenlerde Psikojenik Faktörlerin Kraniyoservikal Ağrı ve Özürlülük Üzerindeki Etkilerinin Araştırılması

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ABSTRACT

Objective: This study aimed to investigate how perceived stress, job burnout and mental fatigue affect neck and craniofacial pain and disability in academics.

Methods: The study included 592 academics with a mean age of 40.11±9.82 years. Neck pain and disability status were determined using the neck disability index (NDI), cranial and facial pain status with the Craniofacial Pain and Disability Index (CFPDI), perceived stress levels with the perceived stress scale-14 (PSS-14), job burnout with the burnout assessment tool (BAT), and mental fatigue was measured using the mental fatigue subscale of the Chalder Fatigue Scale (CFS-mental).

Results: Moderate positive correlations were found between the NDI and PSS-14, BAT, and CFS-mental (r=0.418-0.573, p<0.001). Weak positive correlations were found between the CFPDI and PSS-14, BAT and CFS-mental scores (r=0.232-0.354, p<0.001). The PSS-14, BAT and CFS parameters explained 34.2% of the variance in NDI and 13.2% of the variance in CFPDI.

Conclusion: Psychogenic factors were found to affect neck and craniofacial pain and disability in academics. Therefore, when treating this professional group, psychogenic factors should be considered.

Keywords: Disability, craniofacial pain, psychology, physiotherapy

ÖZ

Amaç: Bu çalışmanın amacı, algılanan stres, iş tükenmişliği ve zihinsel yorgunluğun akademisyenlerde boyun ve kraniyofasiyal ağrı ve sakatlığı nasıl etkilediğini araştırmaktır.

Yöntemler: Çalışmaya yaş ortalaması 40,11±9,82 yıl olan 592 akademisyen dahil edilmiştir. Boyun ağrısı ve engellilik durumu boyun özür indeksi (BÖİ), kraniyal ve yüz ağrısı durumu Kraniyofasiyal Ağrı ve Özürlülük İndeksi (KAÖİ), algılanan stres düzeyleri algılanan stres ölçeği 14 (ASS-14), iş tükenmişliği tükenmişlik değerlendirme aracı (TDA) ve zihinsel yorgunluk Chalder Yorgunluk Ölçeği'nin mental yorgunluk alt ölçeği (CYÖ-mental) kullanılarak ölçülmüştür.

Bulgular: BÖİ ile ASS-14, TDA ve CYÖ-mental arasında orta düzeyde pozitif korelasyon bulundu (r=0,418-0,573, p<0,001). KAÖ ile ASS-14, TDA ve CYÖ-mental puanları arasında zayıf pozitif korelasyon bulunmuştur (r=0,232-0,354, p<0,001). ASS-14, TDA ve CYÖ-mental parametreleri BÖİ'deki varyansın %34,2'sini ve KAÖİ'deki varyansın %13,2'sini açıklamıştır.

Sonuç: Psikojenik faktörlerin akademisyenlerde boyun ve kraniyofasiyal ağrı ve sakatlığı etkilediği bulunmuştur. Bu nedenle, bu meslek grubunu tedavi ederken psikojenik faktörler göz önünde bulundurulmalıdır.

Anahtar Kelimeler: Özür, kraniyofasiyal ağrı, psikoloji, fizyoterapi

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Introduction

Depressive symptoms are one of the most common global health problems, which are thought to affect around 264 million people worldwide. This rate varies between 5.5% and 29.5% among academic staff, and it has been reported that 5.5% of academic staff are employed at private universities experience burnout syndrome (1,2). An excessive workload, demanding job responsibilities, and the pressure to advance academically have all been linked to psychological stress (3,4). Moreover, it is evident that diminished job satisfaction and disagreements with colleagues are known to intensify depressive symptoms within the academic population. Due to the high mental effort involved, constant pressure to perform, the obligation to publish, and institutional responsibilities, academic life can cause intense stress and feelings of burnout in individuals (5).

Neck pain is a very widespread musculoskeletal problem, affecting between 40.4% and 80.1% of academic staff (5). Among the psychogenic causes of neck pain, chronic stress, anxiety, depression, and burnout syndrome are cited as factors.

It has been emphasized that psychogenic factors may be an important risk factor in the onset and development of craniofacial pain (6). Another study reported that craniofacial pain is closely related to psychological factors (7).

There is an increasing body of evidence in the literature suggesting that psychological factors may be associated with musculoskeletal problems, particularly those affecting the craniofacial region and neck (8,9). However, no studies could be found in the literature that have examined the severity of neck and craniofacial pain experienced by academics from a broad psychological perspective.

The aim of this study was to investigate the effects of perceived stress levels, professional burnout, and mental fatigue on craniofacial and neck pain and disability severity among academics working at universities.

Methods

Participants

The study included 592 academics, comprising 304 females and 288 males with an average age of 40.11 years ±9.82 years. All the participants were reached via Google Forms, and all were academics working at higher education institutions. The participants were academic staff working in the departments of physical therapy and rehabilitation, nursing, occupational therapy, child development, and audiology at a total of 32 universities in the Central Anatolia region. Data were collected between June 1, 2025, and October 1, 2025. Participants were contacted by sending invitations to the email addresses listed on their institutions' websites.

A total of 3,602 participants were reached. The response rate for the study was 17.62%. A total of 43 participants were excluded from the study due to missing data. Participants aged 25-65 years who had been working as academics for at least 1 year were included. Individuals with any neurological or rheumatological disease and those with a history of surgery in the neck and craniofacial region, were not included in the study.

This study was also approved by the Research Ethics Committee of Hacettepe University Faculty of Physiotherapy and Rehabilitation (decision no: FTREK25/70, date: 29.05.2025). Informed consent was obtained from all participants.

Evaluations

The age, height, weight, academic experience, and additional medical conditions of all the participants included in the study were recorded.

Self-reported Outcomes

The perceived stress scale-14(PSS-14) was used to measure the emotional stress levels of the study participants. This 14-item scale is used to assess an individual's perceived psychological state, with each item scored on a 5-point Likert scale, ranging from 0 (never) to 4 (very often), to give a total possible score of 56 points (10).

The burnout assessment tool (BAT) was used to assess levels of burnout. This questionnaire, developed by Schaufeli et al. (11), in 2004, consists of six factors and 34 questions. The responses are scored from 1=never to 5=always, with a higher score representing greater burnout, while a low score represents less burnout.

The mental fatigue levels of the participants were assessed with the mental fatigue sub-parameter of the Chalder Fatigue Scale (CFS). The mental fatigue sub-section consists of 4 questions in total, with responses scored on a four-point Likert scale (less than usual, as much as usual, more than usual, much more than usual), in the range of 0 to 3 points, to give a total score of 0 to 12 points. Higher scores suggest more severe fatigue (12).

The neck disability index (NDI) consists of 10 items, 4 of which are related to subjective symptoms and 6 of which are related to activities of daily living. In each section, there are 6 different options for the patient to rate their condition The scoring ranges from 0-5 points for each item providing a maximum score of 50. Higher scores indicate more severe levels of disability (13).

The assessment of pain and resulting disability involving the facial structures and the entire cranium was performed using the 21-item Craniofacial Pain and Disability Index (CFPDI). The total score of this questionnaire ranges from 0 to 63 points, with higher scores indicating more severe pain and disability (14).

Statistical Analysis

Data were analyzed statistically using IBM SPSS version 21.0 software. Conformity to parametric conditions was examined with the Shapiro-Wilk test and all data were seen to be normally distributed. Numerical variables were stated as mean ± standard deviation and minimum-maximum values, and categorical data were reported as number (n) and percentage (%). Correlations between parameters were evaluated with Pearson correlation coefficients. Multiple linear regression was performed to determine the independent variables that contributed significantly to the variance in NDI and CFPDI data. A value of $p<0.05$ was accepted as the level of statistical significance.

Results

The demographic characteristics of the participants and the total scores obtained in the assessment scales are shown in Table 1.

The average age of participants included in the study was 40.11 years, their height was 166.18 cm, their body weight was 68.42 kg, work experience in academia was 12.89 years, PSS-14 scores were 30.03 points, BAT scores were 94.60 points, CFS (mental) scores were 5.42 points, NDI scores were 12.73 points, and CFPDI scores were 10.21 points. All values are given as averages.

Table 1. Demographic data and scale scores of the study participants

n=592	Min-max	Mean ± SD
Age (years)	26-64	40.11±9.82
Height (cm)	148-197	166.18±8.04
Weight (kg)	44-124	68.43±14.88
Duration of working in academia (years)	1-41	12.89±9.43
PSS-14 (points)	9-56	30.03±6.86
BAT (points)	43-163	94.60±22.14
CFS (mental) (points)	0-12	5.42±2.50
NDI (points)	2-42	12.73±6.38
CFPDI (points)	3-59	10.21±7.78

SD: Standard deviation, PSS-14: Perceived stress scale-14, BAT: Burnout assessment tool, CFS (mental): Mental fatigue subscale of the Chalder Fatigue Scale, NDI: Neck disability index, CFPDI: Craniofacial Pain and Disability Index

Correlation analysis revealed significant positive correlations between the NDI and the PSS-14 ($r=0.417$, $p<0.001$), between the NDI and the BAT ($r=0.573$, $p<0.001$), and between the NDI and the CFS-mental ($r=0.418$, $p<0.001$). A significant positive correlation was found between PSS-14 and BAT ($r=0.653$, $p<0.001$) and between PSS-14 and CFS (mental) ($r=0.417$, $p<0.001$). Similarly, a significant positive correlation was observed between BAT and CFS (mental) ($r=0.554$, $p<0.001$) (Table 2).

Correlation analysis revealed significant positive correlations between the CFPDI and PSS-14 ($r=0.232$, $p<0.001$), between CFPDI and BAT ($r=0.354$, $p<0.001$), and between CFPDI and CFS (mental) ($r=0.282$, $p<0.001$). A significant positive correlation was found between PSS-14 and BAT ($r=0.653$, $p<0.001$) and between PSS-14 and CFS (mental) ($r=0.417$, $p<0.001$). Similarly, a significant positive correlation was observed between BAT and CFS (mental) ($r=0.554$, $p<0.001$) (Table 3).

The results of the regression analysis with NDI and CFPDI as dependent variables are given in Table 4. The first model, in which PSS, BAT, and CFS-mental are independent variables, explained 34.2% of the variance in NDI, while the second model explained 13.2% of the variance in CFPDI.

Discussion

The aim of this study was to examine how perceived stress levels, job burnout, and mental fatigue affect craniofacial pain and disability in academic staff. Previous studies have shown that perceived stress, burnout and mental fatigue are associated with neck and craniofacial pain and disability. These psychogenic factors have been found to partially affect craniofacial pain and disability, particularly in cases of neck pain. The original value of this study can be considered to be that it reveals the effects of various psychogenic factors on neck and craniofacial pain, which are quite common in this occupational group, given that academics are a professional group with various psychological risk factors and that the study was conducted on a large sample size. Moreover, the original value of this study is increased by the fact that the factors examined were studied in a professional group on which very limited research has been conducted.

It has been emphasized that pain is partly an emotional experience (15). Vogt and Sikes (16) reported that the medial pain system, which is part of the lateral and medial

Table 2. Pearson correlation coefficients showing associations among the NDI, PSS-14, BAT, and mental fatigue scores

n=592	NDI	PSS-14	BAT	CFS (mental)
NDI		0.417*	0.573*	0.418*
PSS-14	0.417*		0.653*	0.416*
BAT	0.573*	0.653*		0.554*
CFS (mental)	0.418*	0.416*	0.554*	

*: $p<0.001$, Pearson correlation, NDI: Neck disability index, PSS-14: Perceived stress scale-14, BAT: Burnout assessment tool, CFS (mental): Mental fatigue subscale of the Chalder Fatigue Scale

pain systems and supports the affective-motivational dimension of pain, extends medially within the spinothalamic system and extends to the cingulate cortex and limbic system, which are very important for emotional processes, via the medial thalamus. However, Kulkarni et al. (17) emphasised that the medial pain system is also closely related to several subcortical regions that play a key role in emotional processing, such as the amygdala, hypothalamus and periaqueductal grey matter. These neurophysiological mechanisms highlight the close relationship between pain and emotional factors.

Studies have found that perceived stress is associated with neck disability (18,19). Mork et al. (20) demonstrated a moderate association between emotional stress and neck pain (21). One of the other factors that increase pain is hormonal changes. Various studies have shown that negative psychogenic factors—such as emotional stress, mental fatigue, and symptoms of burnout—lower serotonin levels and increase cortisol levels in the body, thereby lowering the pain threshold. However, attributing pain solely to this cause-and-effect relationship would not be an accurate approach. These changes in serotonin and cortisol levels may be only one of the factors affecting pain (22,23). It has been suggested that factors such as stress and depressive symptoms may cause changes in the central pain processing at the spinal cord, medulla oblongata, or cortical levels, which in turn may lead to hyperalgesia (24). The factors mentioned above may be among the reasons why negative psychogenic factors show a positive correlation with neck pain, and regression analysis has shown that they partially explain this pain. However, it has also been emphasized that such negative psychogenic factors can increase muscle tone, and that increased muscle tone can cause various musculoskeletal pains, such as neck pain. In this case, it may again be just one of the factors contributing to increased pain (25). In a study by Kivimäki et al. (26) a four-fold increase in new cases of musculoskeletal pain was found among employees exposed to workplace bullying, and a two-fold increase among those with high workloads and low decision-making autonomy. Therefore, it was concluded that work-related stress factors may trigger or exacerbate pain.

Similarly, craniofacial pain has been reported to be associated with psychogenic factors. Craniofacial pain and disability is a health problem characterised by cranial pain, primarily temporomandibular dysfunction (TMD). As stated by Turk and Rudy (27), one of the main symptoms of TMD is pain, and the management of this is made more difficult by emotional stress and depressive symptoms. Schwartz (28) also suggested that emotional stress is a key contributor to spasms and myofascial pain, particularly in the masticatory muscles.

There are many recent publications on the psychosocial aspects of pain. Grünenwald et al. (29) noted that patients with chronic pain had lower well-being and social belonging, and higher depression. However, they explained the relationship between chronic pain and depression in terms of stress perception and inadequate coping. Fillingim et al. (30) have worked on blood immunological tests, bone and brain imaging, and biomarkers obtained from genetics. In this study, which was conducted with a very large sample size, it was emphasized that biological markers alone are not sufficient for predicting chronic pain and that psychosocial factors must be taken into account. In conclusion, it has been emphasized that a biopsychosocial approach will enable a better understanding of the pain experience in medical conditions. In a study conducted by Chen et al. (31) they examined changes in the amygdala structure in patients with chronic pain and accompanying emotional stress (depression/anxiety). A significant reduction in right amygdala size has been demonstrated in patients with chronic pain and emotional stress. It is emphasized that chronic pain is not merely a sensory experience, but also a source of stress that causes structural changes in emotional processing centers such as the amygdala. It has been noted that these findings once again emphasize that pain and emotional health are intertwined. In their published article, Eich et al. (32) state that for the effective management of chronic pain, psychosocial factors must be recognized, and interdisciplinary, multimodal treatment approaches must

Table 3. Pearson correlation coefficients for associations among the CFPDI, PSS-14, BAT, and CFS (mental) scores

n=592	CFPDI	PSS-14	BAT	CFS (mental)
CFPDI		0.232*	0.354*	0.282*
PSS-14	0.232*		0.653*	0.416*
BAT	0.354*	0.653*		0.554*
CFS (mental)	0.282*	0.416*	0.554*	

*: p<0.001, Pearson correlation, CFPDI: Craniofacial Pain and Disability Index, PSS-14: Perceived stress scale-14, BAT: Burnout assessment tool, CFS (mental): Mental fatigue subscale of the Chalder Fatigue Scale

Table 4. Regression analysis with ndi and CFPDI as the dependent variables

	NDI				CFPDI			
	β	t	p	R^2	β	t	p	R^2
PSS-14	0.055	1.336	0.182	0.342	-0.015	-0.258	0.796	0.132
BAT	0.132	9.509	0.000*		0.103	5.308	<0.001*	
CFS (mental)	0.357	3.477	<0.001*		0.390	2.710	0.007*	

*: p<0.001, NDI: Neck disability index, CFPDI: Craniofacial Pain and Disability Index, PSS-14: Perceived stress scale-14, BAT: Burnout assessment tool, CFS (mental): Mental fatigue subscale of the Chalder Fatigue Scale

be structurally, financially, and educationally supported and consistently integrated into clinical practice. In this way, they have emphasized that both the quality of care will increase and long-term social costs will decrease.

Study Limitations

The fact that craniocervical and neck pain barriers were assessed solely through self-reported questionnaires, the lack of clinical assessment (e.g., physical examination, EMG measurements, imaging methods), and the inability to establish cause-and-effect relationships due to single-time cross-sectional data collection can be considered limitations of this study. The wide range of ages and academic experience of the participating academics can also be considered a limitation.

Finally, another limitation is that no information is provided about the participants' regional distribution, field, or level (research assistant, faculty member, etc.).

Conclusion

The model explained 34.2% of the variance in NDI and 13.2% of the variance in CFPDI. Psychogenic factors should be considered when treating these two issues. Nevertheless, there remains a need for further studies using more objective methods in groups with high emotional stress levels, such as academics.

Ethics

Ethics Committee Approval: This study was also approved by the Research Ethics Committee of Hacettepe University Faculty of Physiotherapy and Rehabilitation (decision no: FTREK25/70, date: 29.05.2025).

Informed Consent: Informed consent was obtained from all participants.

Footnotes

Authorship Contributions

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

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Original Article

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Clinical Image Correction for Extraocular and Periocular Pathologies and Appearance-related Findings Via an AI-based Image-editing Tool

Yapay Zeka Tabanlı Görüntü Düzenleme Aracı ile Ekstraoküler ve Perioküler Patolojiler ve Görünümle İlişkili Bulgularında Klinik Görüntülerinin Düzeltilmesi

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ABSTRACT

Objective: To evaluate the pathology-specific correction performance and photorealistic output quality of the Gemini 2.5 Flash Image model (also known as "Nano Banana"; Google LLC, Mountain View, CA, USA) across multiple periocular and extraocular pathologies and appearance-related findings.

Methods: This retrospective study included 45 standardized clinical photographs representing nine periocular/extraocular pathologies and appearance-related findings. Each image underwent single-step, prompt-based editing using Gemini 2.5 Flash Image. Two independent raters scored images on pathology correction (Q1) and naturalness (Q2) using 5-point Likert scales. Ordinal statistics, Gwet's agreement coefficient (AC), and multilevel cumulative logistic models were applied.

Results: Median scores were high for both Q1 and Q2 across raters. Images rated ≥4 ranged from 84-91% for Q1 and reached 100% for Q2. Interrater agreement was excellent (Q1 AC=0.9466; Q2 AC=0.9878). Highest correction performance was observed for blepharoptosis and exotropia, while lower eyelid blepharoplasty need and thyroid eye disease showed comparatively reduced correction.

ÖZ

Amaç: Bu çalışmanın amacı Gemini 2.5 Flash Image modelinin (Nano Banana; Google LLC, Mountain View, CA, ABD) çoklu perioküler ve ekstraoküler patoloji ve görünümle ilişkili bulguların klinik görüntülerinin düzeltme performansını ve gerçekliğe yakın görüntü üretebilme yeteneğini değerlendirmektir.

Yöntemler: Bu retrospektif çalışma, dokuz perioküler/ekstraoküler patolojiyi ve görünümle ilişkili bulgularını temsil eden 45 standart klinik fotoğrafı içermektedir. Her görüntü, Gemini 2.5 Flash Image kullanılarak tek adımlı, patolojiye özgü metin komutlarıyla düzenlenmiştir. İki bağımsız değerlendirici, görüntüleri patoloji düzeltme (Q1) ve doğallık (Q2) açısından 5'li Likert ölçeği ile skorlamıştır. Ordinal istatistikler, Gwet'in uyum katsayısı (AC) ve çok düzeyli kümülatif lojistik modeller kullanılmıştır.

Bulgular: Her iki değerlendiricide de Q1 ve Q2 için medyan skorlar yüksekti. Q1'de ≥4 puan alan görüntülerin oranı %84-91 iken, Q2'de tüm görüntüler %100 olarak değerlendirildi. Gözlemciler arası uyum mükemmeldi (Q1 AC=0,9466; Q2 AC=0,9878). En yüksek düzeltme performansı blefaroptoz ve ekzotropya olgularında gözlenirken, alt kapak blefaroplasti

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ABSTRACT

Conclusion: Prompt based large language models enabled editing provided clinically meaningful correction with high photorealism across most pathologies, suggesting a practical alternative to dataset dependent conventional image generation approaches.

Keywords: Artificial intelligence, image editing, periocular/extraocular pathology correction, Gemini 2.5 Flash Image, image processing computer-assisted, Nano Banana

ÖZ

ihtiyacı olan olgularda ve tiroid okülopatili olgularda göreceli olarak daha düşük düzeltme elde edildi.

Sonuç: Metin komutlarına dayalı büyük dil modeli tabanlı görüntü düzenleme yaklaşımı, çoğu patolojide yüksek gerçekçilik ile birlikte klinik olarak anlamlı düzeltme sağlamıştır. Bu yöntem, geniş veri setlerine bağımlı geleneksel görüntü üretme modellerine pratik bir alternatif olarak görünmektedir.

Anahtar Kelimeler: Yapay zeka, görüntü düzenleme, perioküler/ekstraoküler patoloji düzeltme, Gemini 2.5 Flash Image, bilgisayar destekli görüntü işleme, Nano Banana

Introduction

The use of generative artificial intelligence (GenAI) for synthetic ocular image generation and editing is increasingly reported in ophthalmology. Most GenAI models, generally based on generative adversarial networks (GANs) and diffusion models, have limited clinical application due to their large-scale training data requirements (1). Visual simulation technologies, which are actively used to predict postoperative appearance, have become an important part of communication with the patient by enabling the prediction of pre- and post-operative appearance, especially in aesthetic surgeries (2-4). However, conventional simulation/editing tools are often time-consuming, costly, and dependent on proprietary software. Additionally, most of these systems fail to produce natural-looking results (5,6). Most GenAI models, generally based on GANs and diffusion models, have limited clinical application due to their large-scale training data requirements. Unlike these traditional approaches, prompt-based editing utilizes the vast pre-trained visual and semantic capabilities of foundation models, thereby overcoming the need for extensive, pathology-specific training datasets (7). New AI models now offer text-to-image (prompt based) and text-guided image editing capabilities; Google Gemini 2.5 Flash Image (also known as "Nano Banana"; Google LLC, Mountain View, CA, USA) is a recent example that can directly edit clinical photographs from textual prompts (8). In the literature, GenAI applications have largely focused on predicting treatment response in intraocular diseases or on single-pathology use cases; also, data on predicting postoperative appearance in periocular procedures are limited. In addition, the fact that the images edited in the previous studies are not evaluated together in terms of both preserving reality and correcting pathology constitutes one of the main limitations in this field (9-13).

This study aims to investigate the correction capacity of the Gemini 2.5 Flash Image model in various periocular/extraocular conditions and appearance-related findings the level of realism of the images produced.

Methods

This single-centered, retrospective study included periocular/extraocular conditions and appearance-related findings; upper eyelid dermatochalasis, the need for lower eyelid blepharoplasty, entropion, ectropion, esotropia, exotropia, brow ptosis, thyroid eye disease, and blepharoptosis. For each condition, images from five patients who presented for treatment were randomly selected, yielding 45 images in total. Inclusion criteria were: presence of one of the listed conditions, availability of a standardized clinical photograph at presentation, and verbal consent for image use and processing via AI systems. Photographs were recorded as JPEGs in the standard RGB color space (quality ≥90) with file size ≥1 megabyte and a short-side dimension ≥1024 pixels. Technical exchangeable image file format metadata (e.g., capture device, exposure settings) were preserved to ensure standardization, while all potentially identifiable personal metadata (e.g., geolocation, patient name) were strictly removed prior to analysis. Images were captured to include the face from the hairline to the subnasal and the target finding, against a homogeneous background, centrally framed, under adequate illumination, without digital zoom, and free of obvious artifacts. All images were taken with an iPhone 16 Pro (Apple Inc., Cupertino, CA, USA). Patients with additional congenital or acquired conditions that could confound periocular/extraocular findings, or with photographs not meeting standardization criteria, were excluded. Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Bezmialem Vakıf University (decision no: 2025/418, date: 22.11.2025); all procedures adhered to the Declaration of Helsinki. Images were uploaded to the Google Gemini 2.5 Flash Image model via the AI studio interface. Access was obtained through a personal account. A separate conversation tab was created for each case, and single-step edits were performed using condition-specific text prompts that requested correction of the target finding while preserving the anatomic and natural appearance of surrounding tissues (full prompt templates are provided in Supplementary Material 1). A single output image was generated for each case. Forty-five images were generated by Gemini 2.5 Flash Image (Figure 1).

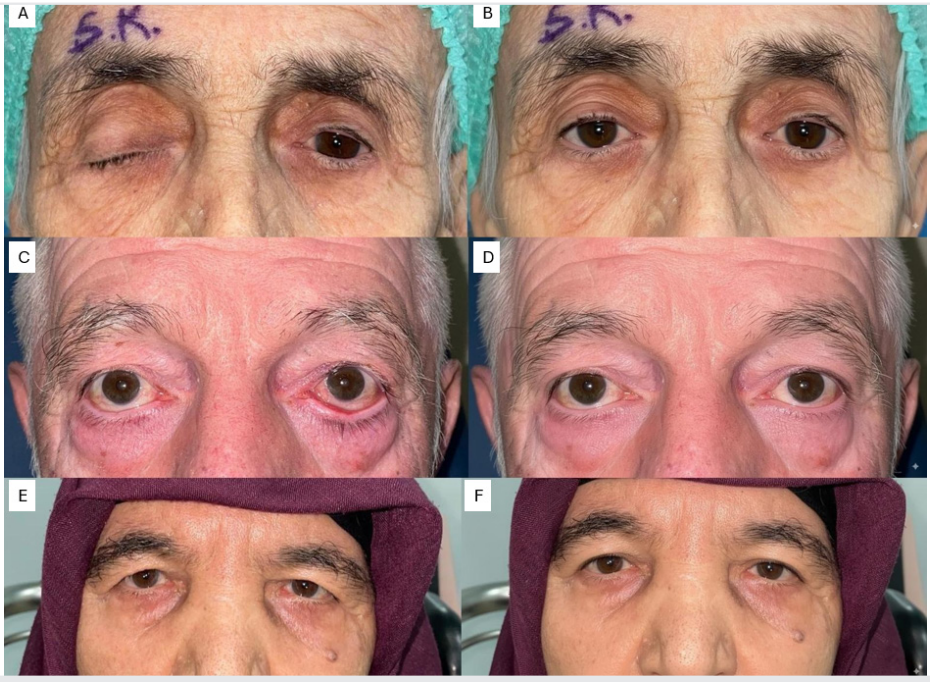

Figure 1. Representative examples of AI-assisted editing in clinical photographs. Original images are shown in A, C, and E, and AI-edited outputs in B, D, and F. A, B: Blepharoptosis; C, D: Ectropion; E, F: Simulated upper eyelid blepharoplasty

The generated images were independently assessed, under randomized presentation order, by an experienced ophthalmologist (Rater 1) and an otorhinolaryngologist with expertise in periocular facial aesthetic surgery (Rater 2). For each image, two questions were scored using a 5-point Likert scale: Q1 (correction of pathology; 1=no correction, 5=complete correction) and Q2 (natural-artificial distinguishability; 1=artificial/inappropriate, 5=completely natural).

Statistical Analysis

All analyses were conducted in Stata v19.0 (StataCorp LLC, College Station, TX, USA). Five-point Likert scores were treated as ordinal; descriptive statistics are reported as median (min-max) and category frequencies n (%). Interrater agreement was summarized using Gwet's agreement coefficient (AC) with ordinal weighting and complementary percent agreement, given their lower sensitivity to marginal imbalance and ceiling effects. To evaluate pathology-specific performance and the effect of the two items (Q1: correction; Q2: naturalness), we fit a multilevel cumulative proportional-odds logistic regression including fixed effects for item (Q1/Q2) and random intercepts for image and rater to account for repeated ratings and between-image heterogeneity. For clinical interpretability, adjusted marginal probabilities were derived for "complete correction" [p (score=5)] and "success" [p (score ≥4)] by pathology and item, with 95% Confidence intervals (CIs) obtained via the delta method. As a secondary robustness check for the binary endpoint (score ≥4), we also fit a Firth-penalized logistic regression. All p-values were two-sided with a significance threshold of $p<0.05$.

Results

A total of 45 AI-edited images (9 conditions ×5 cases) were scored by two independent doctors on two items (Q1: correction; Q2: naturalness). Median (min-max) scores were 5 (3-5) for Q1 and 5 (4-5) for Q2 for Rater 1, and 4 (2-5) for Q1 and 5 (4-5) for Q2 for Rater 2. The proportion of images rated ≥4 was 84.44% (Q1) and 100% (Q2) for Rater 1, and 91.11% (Q1) and 100% (Q2) for Rater 2 (Table 1). Interrater agreement was very high: for Q1, weighted percent agreement was 97.64% and Gwet's AC was 0.9466; for Q2, 99.03% and 0.9878, respectively.

According to Q1 medians, "need for lower lid blepharoplasty" was selected as the reference category because it had the lowest improvement scores (Rater1/Rater2: 3/4); other pathologies were browlift 5/4, ectropion 5/4, entropion 5/5, esotropia 5/4, ptosis 5/5, thyroid ophthalmopathy 4/4, upper lid blepharoplasty 4/5, exotropia 5/5, respectively. The probability of being in higher score categories compared to the reference was significantly increased for ptosis and exotropia [odds ratio (OR)=327.62; p=0.001]; while OR=26.38 (p=0.013) was observed as OR=22.25 (p=0.018) for browlift and esotropia and OR=22.25 (p=0.018) for entropion; a marginal increase was observed in upper eyelid blepharoplasty (OR=9.74; p=0.065), but no significant difference was observed in ectropion (OR=4.98; p=0.182) and thyroid ophthalmopathy (OR=1.78; p=0.619). The item effect favored Q2: compared with Q1, Q2 substantially increased the probability of assigning higher scores (Q2 vs. Q1 OR=34.53; 95% CI: 9.68-123.18; p<0.001), indicating that the same images were rated meaningfully higher when evaluated for naturalness (Table 2).

Table 1. Rater-wise distribution of 5-point Likert scores for pathology correction (Q1) and image naturalness (Q2) in AI-edited periocular/extraocular clinical photographs (n=45 images), reported as median (min-max) and category frequencies

Rater	Item	n	Median (min-max)	Score=2	Score=3	Score=4	Score=5
Rater 1	Q1 - Correction of pathology	45	5 (3-5)	-	15.56%	33.33%	51.11%
Rater 1	Q2 - Naturalness	45	5 (4-5)	-	-	15.56%	84.44%
Rater 2	Q1 - Correction of pathology	45	4 (2-5)	2.22%	6.67%	42.22%	48.89%
Rater 2	Q2 - Naturalness	45	5 (4-5)	-	-	8.89%	91.11%
All	(Q1+Q2, both raters combined)	180	5 (2-5)	0.56%	5.56%	25.00%	68.89%

Q1: Question 1, Q2: Question 2, AI: Artificial intelligence

Model-based adjusted probabilities indicated that, under Q1 (correction), the likelihood of "complete correction" (p=5) was highest for ptosis and exotropia (=0.90), followed by brow ptosis and esotropia (=0.57), entropion (=0.54), upper-eyelid blepharoplasty/dermatochalasis (=0.40), ectropion (=0.29), thyroid eye disease (=0.15), and lowest for lower-eyelid blepharoplasty need (=0.10). Under Q2 (naturalness), these values increased across all pathologies: ptosis/exotropia =0.996; brow ptosis/esotropia =0.956; entropion =0.950; upper eyelid =0.904; ectropion =0.845; thyroid eye disease =0.714; lower eyelid =0.620 (Table 3). At the "success" threshold (p≥4), adjusted probabilities were very high for most conditions: ptosis/exotropia =0.998; brow ptosis/esotropia =0.978; entropion =0.975; upper eyelid =0.951; ectropion =0.920; with comparatively lower values for lower eyelid =0.795 and thyroid eye disease =0.849. When restricted to Q1, the ranking was preserved but separations became more pronounced (ptosis/exotropia =0.996; brow ptosis/esotropia =0.955; entropion/upper eyelid =0.864-0.905; ectropion =0.848; thyroid =0.717; lower eyelid =0.625). For Q2, p≥4 exceeded 0.96 for all pathologies (Table 4).

Discussion

In this study, the Gemini 2.5 Flash Image model was applied to patient photographs across nine extraocular/periocular conditions using text-based prompts to perform targeted image editing, and its correction performance was evaluated by two independent physicians. The findings indicate that the model produced clinically meaningful results in several conditions, with the highest performance observed in blepharoptosis and exotropia, and comparatively limited effectiveness in lower eyelid blepharoplasty requirement and thyroid eye disease.

In the current literature, AI-assisted image generation/editing studies predominantly focus on a single pathology or employ GAN/diffusion-based models trained on large datasets. Indeed, a recent study developed a deep learning system to predict postoperative appearance after blepharoptosis surgery using a dataset of 362 patients, reporting patient-satisfying postoperative simulations based on both objective measurements and clinician/patient satisfaction surveys. The authors further emphasized the practical benefits of this approach for managing patient expectations, supporting clinician counseling, and reducing preoperative anxiety (14). In a related study, postoperative appearance after orbital decompression for thyroid eye disease was simulated using a GAN and evaluated on 109 matched pre-postoperative facial image pairs. While the authors highlighted the model's potential for patient counseling, the images were compiled from Google and synthesized at relatively low resolution (64×64 pixels), resulting in outputs that lacked realism and appeared low quality (15). There are also studies in other fields in terms of generating images with the GAN models. For example, postoperative soft-tissue changes

Table 2. Multilevel cumulative proportional-odds logistic regression results for pathology categories (reference: lower eyelid blepharoplasty) and item effect (Q2 vs. Q1)

Variable (ref: Lower eyelid blepharoplasty: Q1)	OR	95% CI	p-value
Brow ptosis/browlift	26.38	2.02-344.06	0.01
Ectropion	4.98	0.47-52.41	0.18
Entropion	22.25	1.68-293.88	0.02
Esotropia	26.38	2.02-344.06	0.01
Upper eyelid ptosis	327.62	10.81-9,925.03	0.001
Thyroid eye disease	1.78	0.18-17.28	0.62
Upper eyelid blepharoplasty/dermatochalasis	9.74	0.87-108.94	0.06
Exotropia	327.62	10.81-9,925.03	0.001
Item: Q2 vs. Q1	34.53	9.68-123.18	<0.001

Q1: Question 1, Q2: Question 2, ref: Reference, OR: Odds ratio, CI: Confidence interval

Table 3. Model-based adjusted marginal probabilities of receiving the maximum score [p (score=5), "complete correction/highest rating"] by pathology and rating item (overall, Q1, and Q2)

Pathology	Overall p (=5) (95% CI)	Q1 p (=5) (95% CI)	Q2 p (=5) (95% CI)
Lower eyelid blepharoplasty indicated	0.362 (0.161-0.562)	0.103 (-0.031-0.238)	0.620 (0.335-0.906)
Brow ptosis/browlift	0.765 (0.571-0.959)	0.574 (0.250-0.897)	0.956 (0.882-1.031)
Ectropion	0.566 (0.350-0.781)	0.286 (0.021-0.552)	0.845 (0.658-1.032)
Entropion	0.747 (0.543-0.950)	0.543 (0.209-0.877)	0.950 (0.866-1.033)
Esotropia	0.765 (0.571-0.959)	0.574 (0.250-0.897)	0.956 (0.882-1.031)
Ptosis	0.949 (0.845-1.052)	0.902 (0.706-1.098)	0.996 (0.984-1.008)
Thyroid eye disease	0.434 (0.223-0.646)	0.155 (–0.028-0.338)	0.714 (0.452-0.975)
Upper eyelid blepharoplasty/dermatochalasis	0.650 (0.437-0.862)	0.396 (0.090-0.702)	0.904 (0.768-1.039)
Exotropia	0.949 (0.845-1.052)	0.902 (0.706-1.098)	0.996 (0.984-1.008)

Q1: Question 1, Q2: Question 2, CI: Confidence interval

Table 4. Model-based adjusted marginal probabilities of meeting the success threshold [p (score=4 or 5)] by pathology and rating item (overall, Q1, and Q2)

Pathology	Overall p (≥4) (95% CI)	Q1 p (≥4) (95% CI)	Q2 p (≥4) (95% CI)
Lower eyelid blepharoplasty indicated	0.795 (0.631-0.960)	0.625 (0.342-0.908)	0.966 (0.912-1.021)
Brow ptosis/browlift	0.978 (0.940-1.016)	0.957 (0.885-1.030)	0.998 (0.995-1.002)
Ectropion	0.920 (0.820-1.020)	0.848 (0.662-1.034)	0.992 (0.977-1.008)
Entropion	0.975 (0.932-1.017)	0.951 (0.870-1.032)	0.998 (0.994-1.002)
Esotropia	0.978 (0.940-1.016)	0.957 (0.885-1.030)	0.998 (0.995-1.002)
Ptosis	0.998 (0.992-1.004)	0.996 (0.984-1.007)	1.000 (0.999-1.000)
Thyroid eye disease	0.849 (0.702-0.995)	0.717 (0.456-0.979)	0.980 (0.944-1.016)
Upper eyelid blepharoplasty/dermatochalasis	0.951 (0.880-1.021)	0.905 (0.772-1.039)	0.996 (0.987-1.005)
Exotropia	0.998 (0.992-1.004)	0.996 (0.984-1.007)	1.000 (0.999-1.000)

Q1: Question 1, Q2: Question 2, CI: Confidence interval

after osteotomy have been predicted using approaches that incorporate comprehensive computed tomography and magnetic resonance imaging data from all patients (16,17). Within ophthalmology, GANs have been used to synthesize or predict imaging across several indications, including retinal architecture after epiretinal membrane surgery, macular anatomy following macular hole surgery, and optic coherence tomography appearances after anti-vascular endothelial growth factor therapy (10,12,18,19).

It is noteworthy that GAN models are used in these studies because their methods are based on large data sets and focus on a specific disease entity. In contrast, we demonstrate that with a much smaller dataset, purely text-guided prompting can effectively drive image editing for multiple extra/periocular appearance-related findings. To avoid degrading fidelity, we analyzed images at a minimum of 1024×1024 pixels, which likely contributed to the clinically credible realism observed. This performance drop can be mechanistically linked to the model's inability to manage volumetric (e.g., fat reduction, hollow formation, maintaining tear trough contour) or multi-planar/3D spatial changes (e.g., correcting proptosis or eyelid-globe relationship) using a single, 2D text prompt. Clinically, this defines the limit where a prompt-based 2D editing tool fails to simulate the complexities of aesthetic surgery and postoperative appearance. Notably, "naturalness" (Q2) scores were consistently higher than "correction" (Q1), indicating that the model not only attempts the correction but also preserves photorealistic appearance. Given that the model achieves near-perfect photorealism even when the clinical correction is poor, caution should be exercised regarding the appropriate use of this tool. For complex procedures where the model's clinical success (Q1) is demonstrated to be low (like lower lid), the high realism (Q2) could potentially create unrealistic patient expectations if the output is mistaken for an achievable post-operative result. Therefore, limiting the use of this single-step AI tool to simple, geometry-focused corrections is advised until further validation in volumetric cases is obtained.

Studies in the literature have focused on GANs, and studies using large language models to generate images from

text are limited (20-22). To our knowledge, there are no studies on editing extraocular/periocular pathology images using prompt-based large language models. One of the strengths of our study is that the performance of the model in different pathologies is reported holistically with two separate evaluations (correction/naturalness).

Study Limitations

Limitations include the absence of direct comparison with true postoperative "outcome" images, the single-center design with a limited number of images, reliance on a single AI model (Gemini 2.5 Flash Image), and assessments based on two items rated by two clinicians who were aware of the target condition, which may have introduced potential expectation bias. Future studies should incorporate blinded assessment (e.g., masking the target condition and randomizing mixed pathology sets) to reduce potential bias. We anticipate progress in this field through future studies that perform quantitative comparisons using matched pre-postoperative pairs for each pathology and conduct multi-center investigations with larger datasets that benchmark different pathologies and AI models head-to-head.

Conclusion

This work suggests that prompt-based, large language model-enabled image editing is a promising tool for extra-/periocular conditions, capable of delivering both clinically meaningful correction and photorealistic appearance. Future research with larger, multi-pathology datasets and diverse algorithms will be important to validate and extend these findings.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Bezmialem Vakıf University (decision no: 2025/418, date: 22.11.2025).

Informed Consent: Verbal informed consent was obtained from all patients for the use of their anonymized clinical photographs.

Declaration Regarding the Use of AI and AI-assisted Technologies

During the preparation of this study, the authors utilized Google Gemini 2.5 Flash Image to generate AI-edited clinical photographs from standardized patient images using predefined pathology-specific prompts. The outputs were systematically reviewed by the authors, and their accuracy, clinical plausibility, and consistency with the original image content were verified before inclusion in the analyses. After carefully reviewing and editing the content as necessary, full responsibility for the publication's scientific and ethical integrity is taken by the authors. The use of this AI tool primarily influenced the generation of edited images used for performance evaluation and the visual dataset supporting the study outcomes.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.P., B.G., H.H., F.K., M.H.Ö., Concept: B.P., B.G., H.H., F.K., M.H.Ö., Design: B.P., B.G., H.H., F.K., M.H.Ö., Data Collection or Processing: B.P., B.G., H.H., M.Ö.K., F.K., Analysis or Interpretation: B.P., F.K., M.H.Ö., Literature Search: B.P., H.H., F.K., Writing: B.P., B.G.

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

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Original Article

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Measuring the Quality of Life of Patients Undergoing Total or Subtotal Gastrectomy Due to Gastric Cancer

Mide Kanseri Nedeniyle Total veya Subtotal Gastrektomi Yapılan Hastaların Yaşam Kalitesini Ölçme

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ABSTRACT

Objective: Gastric cancer is prevalent both globally and in Türkiye. The primary treatment for this condition is surgical resection. However, because the stomach plays a vital role in the digestive system, its removal can lead to significant morbidity and mortality, as well as considerable alterations in post-operative quality of life. To address these changes, questionnaires such as the EORTC QLQ-C30 and EORTC STO22 have been developed to assess physical, social, and psychological well-being.

Methods: The quality of life of patients who underwent surgery for gastric cancer at Bezmialem University Faculty of Medicine was assessed using the EORTC QLQ-C30 and EORTC STO22 questionnaires, which are commonly utilized for measuring quality of life in Europe. Following the approval of the non-interventional ethics committee on July 10, 2018 (approval no: 15/183), a retrospective review was conducted of patients diagnosed with gastric cancer who had undergone either total or subtotal gastrectomy between October 2010 and April 2018. Demographic, pathological, and surgical data were collected. Eighty-five surviving patients, who were at least three months post-adjuvant therapy and free of recurrence, were contacted to participate. The Turkish versions of the EORTC QLQ-C30 and EORTC STO22 questionnaires were administered prospectively. Subsequently, statistical methods were employed to compare the total gastrectomy and subtotal gastrectomy groups.

Results: A comparison was conducted between the pathologies and quality of life of 43 patients who underwent total gastrectomy and 42 patients who had

ÖZ

Amaç: Mide kanseri hem dünyada hem de Türkiye'de yüksek sıklıkta görülmektedir. En önemli tedavisi cerrahi rezeksiyondur. Ancak midenin sindirim sisteminde çok önemli bir role sahip olması; rezeksiyon sonrası morbidite ve mortalitenin yanında yaşam kalitesinde de anlamlı değişiklikler meydana getirmesine neden olmaktadır. Bu amaçla, hastalara yönelik fiziksel, sosyal ve psikolojik iyilik halini ölçen anketler hazırlanmıştır. EORTC QLQ-C30, EORTC STO22 bu anketlerden bazılarıdır.

Yöntemler: Bezmialem Vakıf Üniversitesi Tıp Fakültesi'nde mide kanseri nedeniyle ameliyat edilen hastaların yaşam kaliteleri ölçüldü. Ölçüm için Avrupa'da yaşam kalitesi için tercih edilen anket EORTC QLQ-C30, EORTC STO22 formları kullanıldı. Çalışma için 10 Temmuz 2018 tarihinde 15/183 numaralı girişimsel olmayan etik kurul onayı alındıktan sonra 2010 Ekim ile 2018 Nisan ayları arasında mide kanseri tanısı ile total veya subtotal gastrektomi ameliyatı yapılmış olan hastalar retrospektif olarak tarandı. Demografi, patoloji ve ameliyat bilgileri not edildi. Bu hastalardan hayatta olanlar ve adjuvan tedavisinin üzerinden en az 3 ay geçmiş olup nüksü olmayan 85 hasta ile irtibata geçildi. Prospektif olarak EORTC QLQ-C30, EORTC STO22 Türkçe formları doldurduldu. Daha sonra total gastrektomi ve subtotal gastrektomi grupları istatistiksel yöntemlerle karşılaştırıldı.

Bulgular: Total gastrektomi yapılmış 43 hasta ile subtotal gastrektomi yapılmış 42 hastanın patolojileri ve yaşam kaliteleri karşılaştırıldı. EORTC QLQ-C30 anketine göre diyare, EORTC STO22 anketine göre ise disfaji total gastrektomi uygulanan hastalarda daha sık görüldü.

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ABSTRACT

subtotal gastrectomy. The results from the EORTC QLQ-C30 questionnaire indicated that diarrhea occurred more frequently in the total gastrectomy group. Additionally, the EORTC STO22 questionnaire revealed a higher incidence of dysphagia in this same group.

Conclusion: Based on this information, it was concluded that patients who underwent subtotal and total gastrectomy experienced a similar global quality of life; however, specific symptoms such as diarrhea and dysphagia were more favorable in the subtotal group. It is recommended that distal subtotal gastrectomy be considered preferable, as long as surgical procedures adhere to oncological standards, since it better preserves patient comfort by limiting these specific postoperative symptoms.

Keywords: Gastric cancer, quality of life, EORTC QLQ-C30, EORTC STO22

ÖZ

Sonuç: Bu bilgiler ışığında, subtotal ve total gastrektomi yapılan hastaların genel yaşam kalitelerinin benzer olduğu, ancak diyare ve disfaji gibi spesifik semptomların total gastrektomi grubunda daha belirgin olduğu tespit edildi. Cerrahi prosedürler onkolojik standartlara uygun olduğu sürece, bu spesifik postoperatif semptomları sınırlayarak hasta konforunu koruduğu için distal subtotal gastrektominin tercih edilmesi önerilmektedir.

Anahtar Kelimeler: Mide kanseri, yaşam kalitesi, EORTC QLQ-C30, EORTC STO22

Introduction

Cancer is a leading cause of death worldwide, responsible for nearly 10 million deaths in 2024, which accounts for almost one in six fatalities. The most common types of cancer include lung, breast, colon and rectum, prostate, and stomach cancers. Gastric cancer is the fifth leading cause of cancer-related deaths for both men and women (1). According to Turkish Cancer Statistics, the gastric cancer mortality rate in Türkiye was 5.9% among men and 3.9% among women in 2020 (2). Various treatment methods exist for gastric cancer depending on its stage after diagnosis. The most important of these treatments is surgical resection. However, the stomach plays a very important role in the digestive system, which leads to significant changes in quality of life (QoL) in addition to morbidity and mortality after resection.

Depending on the location of the tumor, total gastrectomy (TG) may be preferred. However, subtotal gastrectomy (SG) is also an option for proximally and distally located tumors. The effects of TG or SG, which are decided based on anatomical localization, on morbidity and QoL have been a constant subject of debate.

To understand which type of surgery is better, it is necessary to consult scales that measure postoperative QoL, besides recurrence and survival. According to the WHO definition, QoL is an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns.

Health-related QoL is defined as a person's perceived wellbeing in physical, mental, and social domains of health (3). Numerous question systems are available in oncology to evaluate and reveal subjective parameters related to QoL. Among these, the Turkish question forms of The European Organization for Research and Treatment of Cancer Quality of Life Core (EORTC QLQ-C30, EORTC STO22) are well-adapted for their comprehensive nature.

For this purpose, the measurement and evaluation of the QoL of patients who underwent total or SG due to gastric cancer at the General Surgery Department of Bezmialem University Faculty of Medicine was planned.

Methods

Thesis Origin and Presentation History

This manuscript is derived from the Thesis of Mehmet Güzel, successfully completed at the Department of General Surgery, Bezmialem University Hospital, İstanbul/Türkiye, in 2019.

Preliminary findings based on this patient cohort were previously presented as an oral and written abstract at the 6th International Congress on Quality of Life in Health (SAYKAD), held in İzmir on November 22-23, 2019.

Study Design

This was a single-center, retrospective cohort study conducted at the Department of General Surgery, Bezmialem University Hospital, İstanbul/Türkiye between October 2010 and April 2018.

Ethics and Consent

The study protocol was reviewed and approved by the Bezmialem University Non-Interventional Ethics Committee on 10.07.2018, with the decision number 15/183.

All procedures adhered strictly to the ethical principles outlined in the Declaration of Helsinki. Informed consent was obtained from all participants prior to their inclusion in the study.

Procedures

Patients who underwent surgery for gastric cancer at the General Surgery Department of Bezmialem University Faculty of Medicine between 2010 and 2018 were selected. These patients, who had undergone TG or SG, were screened from the hospital's online registration system. Survivors were called by phone and invited to the hospital.

The study was explained to the patient in the general surgery outpatient clinic room. After obtaining their consent, they were given the Turkish translated versions of the EORTC-QLQ30 and EORTC- STOCH 22 questionnaire forms. The questionnaire forms were filled out. The results obtained were compared with both the type of surgery and the pathology results of the patients.

During the period between October 2010 and April 2018, gastrectomy for gastric cancer was performed on 265 patients in our clinic. Of these, 161 (60%) patients underwent TG, and 104 (40%) patients underwent SG.

Out of these 265 patients, 153 died, and 27 patients could not be reached. The remaining 85 patients were called to the outpatient clinic. In the clinic, after explaining the study to the patient and obtaining consent, the questionnaires were applied. The completed questionnaires were processed.

Inclusion Criteria

- All patients who were diagnosed with gastric cancer, underwent surgery between 2010 and 2018, and were at least 3 months post-operation.
- Patients who were at least 3 months post-adjuvant treatment.

Exclusion Criteria

- Patients who were operated on for gastric cancer and died.
- Patients who were psychiatrically dependent on external support.
- Patients who were hospitalized for another disease during the examination period.
- Receiving chemotherapy or radiotherapy.

Statistical Analysis

Mean standard deviation and percentage were used for descriptive statistics of the groups. In intergroup comparisons:

- The Student's t-test was used when comparing means.
- The chi-square test or Fisher's exact test was used when comparing categorical data.
- The Spearman correlation coefficient was used when examining intragroup relationships.
- The significance level was accepted as 0.05 for all tests.

Results

The mean age of patients was 56.6 in the SG group and 60.09 in the TG group. The cohort consisted of 59 men (69.4%) and 26 women (30.6%). No significant difference was detected in age or gender.

The postoperative length of hospital stay was measured as an average of 7 days for SG group and 6.95 days for TG group, with no significant difference found. The mean operation time was 223.21 minutes in the SG group and 239.40 minutes in the TG group; this difference was found to be statistically significant (p=0.035, Table 1), showing that SG procedures were associated with significantly shorter operative durations.

The tumor diameter was measured as an average of 3.85 cm in SG group and 6.38 cm in TG group. A significant difference was found (p<0.001). Accordingly, the tumor size was significantly larger in TG group.

The number of lymph nodes was measured as an average of 32.1 in SG group and 35.42 in TG group, with no significant difference found. The number of positive lymph nodes was measured as an average of 5.4 in SG group and 5.79 in TG group, with no significant difference found.

Demographic and pathological data for the two groups are presented (Tables 1 and 2) .

When pathological examinations were reviewed, diffuse and intestinal type adenocarcinomas were found to be significantly higher compared to mixed-type adenocarcinomas.

In SG group, tumors in the antropyloric region were found to be higher than those in the cardia and corpus. However, in TG group, no significant difference was observed between the locations. The lack of a significant difference between regions in TG group may be attributed to the fact that TG was also performed for tumors in the cardia region in the clinic.

Table 1. Characteristics of the groups

Characteristic	Group	Mean ± SD	p-value
Age (years)	Subtotal	56.90±11.78	0.162
	Total	60.09±8.91	
Length of hospital stay (days)	Subtotal	7.00±2.57	0.925
	Total	6.95±1.94	
Operation time (min)	Subtotal	223.21±29.15	**0.035**
	Total	239.40±39.51	
Tumor diameter (cm)	Subtotal	3.85±1.93	**<0.001**
	Total	6.38±3.83	
Lymph node count	Subtotal	32.10±12.63	0.372
	Total	35.42±20.52	
Positive lymph node count	Subtotal	5.14±7.53	0.691
	Total	5.79±7.47	

SD: Standard deviation

Table 2. Characteristics of the groups

Variable	Subtotal (n=42)	Total (n=43)	Overall (n=85)	p-value
Gender, n (%)				0.311
Male	27 (64.3%)	32 (74.4%)	59 (69.4%)	
Female	15 (35.7%)	11 (25.6%)	26 (30.6%)	
Prior abdominal surgery, n (%)				0.635
Yes	8 (19.0%)	10 (23.3%)	18 (21.2%)	
No	34 (81.0%)	33 (76.7%)	67 (78.8%)	
Presence of GI complaints, n (%)				0.892
Yes	26 (61.9%)	26 (60.5%)	52 (61.2%)	
No	16 (38.1%)	17 (39.5%)	33 (38.8%)	
Comorbidity, n (%)				0.64
Yes	20 (47.6%)	29 (67.4%)	49 (57.6%)	
No	22 (52.4%)	14 (32.6%)	36 (42.4%)	
Tumor location, n (%)				<0.001
Antro-pyloric	34 (81.0%)	2 (4.7%)	36 (42.4%)	
Cardia	0 (0.0%)	15 (34.9%)	15 (17.6%)	
Corpus	8 (19.0%)	26 (60.5%)	34 (40.0%)	
Lymph node dissection, n (%)				0.273
D1	5 (11.9%)	2 (4.7%)	7 (8.2%)	
D2	36 (85.7%)	41 (95.3%)	77 (90.6%)	
D3	1 (2.4%)	0 (0.0%)	1 (1.2%)	
Pathological tumor stage, n (%)				0.340
Stage 1	11 (26.2%)	6 (14.0%)	17 (20.0%)	
Stage 2	13 (31.0%)	12 (27.9%)	25 (29.4%)	
Stage 3	18 (42.9%)	24 (55.8%)	42 (49.4%)	
Stage 4	0 (0.0%)	1 (2.3%)	1 (1.2%)	
Lauren classification, n (%)				0.34
Diffuse	20 (47.6%)	31 (72.1%)	51 (60.0%)	
Intestinal	20 (47.6%)	9 (20.9%)	29 (34.1%)	
Mixed	2 (4.8%)	3 (7.0%)	5 (5.9%)	
Lymphovascular invasion, n (%)				0.929
Yes	25 (59.5%)	26 (60.5%)	51 (60.0%)	
No	17 (40.5%)	17 (39.5%)	34 (40.0%)	
Perineural invasion, n (%)				0.561
Yes	27 (64.3%)	25 (58.1%)	52 (61.2%)	
No	15 (35.7%)	18 (41.9%)	33 (38.8%)	
Tumor histological type, n (%)				0.540
Adenocarcinoma	31 (73.8%)	32 (74.4%)	63 (74.1%)	
Mixed	1 (2.4%)	3 (7.0%)	4 (4.7%)	
Signet ring cell carcinoma	10 (23.8%)	8 (18.6%)	18 (21.2%)	
Postoperative complication, n (%)				0.494
Yes	1 (2.4%)	0 (0.0%)	1 (1.2%)	
No	41 (97.6%)	43 (100.0%)	84 (98.8%)	
Adjuvant therapy, n (%)				<0.001
Yes	26 (61.9%)	43 (100.0%)	69 (81.2%)	
No	16 (38.1%)	0 (0.0%)	16 (18.8%)	

Percentages are calculated vertically based on individual surgical subgroup total sizes (n=42 for subtotal, n=43 for total, and n=85 for overall). Statistical significance was determined using the chi-square test or Fisher's exact test where applicable
GI: Gastrointestinal

No significant difference was observed based on the type of surgery regarding the positivity of lymphovascular and perineural invasion.

When pathological staging was examined, the proportion of Stage 1, Stage 2, and Stage 3 patients was found to be significantly higher than Stage 4 patients. The reason for this can be attributed to the early death of Stage 4 patients, which prevented their inclusion in the study.

When the two groups were compared, a significant difference was observed in diarrhea (DI) in the EORTC QLQ 30 test, with p<0.01. Accordingly, patients who underwent TG had significantly higher complaints of DI compared to patients who underwent SG. No significant difference was observed in the other scales (Table 3).

When the two groups were compared according to the EORTC STO22 test, a significant difference was observed in dysphagia with p<0.05. Accordingly, patients who underwent TG had significantly higher complaints of

Table 3. EORTC QLQ-C30 questionnaire statistics

Scale	Group	Mean	SD	T-test for equality of means		
				t	p-value	
QL (Global QoL)	SG	72.62	21.49	0.032	0.975	>0.05
	TG	72.48	18.59			
PF (Physical functioning)	SG	85.24	17.95	1.950	0.055	>0.05
	TG	77.67	17.81			
RF (Role functioning)	SG	82.94	29.10	-0.529	0.598	>0.05
	TG	85.66	16.90			
EF (Emotional functioning)	SG	72.42	20.54	-0.282	0.779	>0.05
	TG	73.84	25.43			
CF (Cognitive functioning)	SG	77.38	15.54	-0.030	0.976	>0.05
	TG	77.52	25.43			
SF (Social functioning)	SG	86.90	29.57	0.015	0.988	>0.05
	TG	86.82	19.44			
FA (Fatigue)	SG	30.42	20.39	-0.452	0.653	>0.05
	TG	32.56	23.05			
NV (Nausea/vomiting)	SG	20.63	21.72	0.708	0.481	>0.05
	TG	17.05	24.80			
PA (Pain)	SG	23.81	21.51	-0.045	0.964	>0.05
	TG	24.03	23.37			
DY (Dyspnea)	SG	11.11	19.01	-0.130	0.897	>0.05
	TG	11.63	17.64			
SL (Sleep disturbance)	SG	18.25	23.52	-0.740	0.462	>0.05
	TG	22.48	28.84			
AP (Appetite loss)	SG	17.46	30.57	-0.908	0.367	>0.05
	TG	24.03	35.88			
CO (Constipation)	SG	14.29	21.01	0.529	0.598	>0.05
	TG	11.63	25.08			
DI (Diarrhea)	SG	5.56	14.57	**-3.685**	**0.000**	**<0.01**
	TG	24.03	29.39			
FI (Financial difficulties)	SG	24.60	29.50	-0.278	0.782	>0.05
	TG	26.36	28.69			

Key finding: Diarrhea (DI) showed a statistically significant difference between the groups (p<0.01), being higher in the total gastrectomy (TG) group
SG: Subtotal gastrectomy, SD: Standard deviation, EORTC STO22 (EORTC QLQ-STO22): European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Gastric Cancer-Specific Module, QoL: Quality of life

Table 4. EORTC STO22 questionnaire statistics

Scale	Group	Mean	SD	T-test for equality of means		
				t	p-value	
BI-F (Body image - function)	SG	82.54	26.79	1.258	0.212	>0.05
	TG	74.42	32.40			
DYS (Dysphagia)	SG	8.47	10.36	**-2.497**	**0.015**	**<0.05**
	TG	16.02	16.85			
PAIN (Pain)	SG	24.60	16.96	0.576	0.566	>0.05
	TG	22.29	19.98			
RFX (Reflux)	SG	22.49	18.28	0.112	0.911	>0.05
	TG	21.96	24.18			
EAT (Eating restriction)	SG	18.45	14.79	-1.509	0.135	>0.05
	TG	24.61	22.04			
ANX (Anxiety)	SG	26.19	23.00	-0.813	0.419	>0.05
	TG	30.49	25.67			
DM (Dry mouth)	SG	25.40	27.36	-0.855	0.395	>0.05
	TG	31.78	32.85			
TA (Taste)	SG	9.52	23.61	-1.882	0.063	>0.05
	TG	20.16	28.30			
BI (Body image - symptom)	SG	17.46	26.79	-1.258	0.212	>0.05
	TG	25.58	32.40			
HL (Hair loss)	SG	18.25	23.52	1.084	0.282	>0.05
	TG	12.79	22.96			

SD: Standard deviation, TG: Total gastrectomy, SG: Subtotal gastrectomy

dysphagia compared to patients who underwent SG. No significant difference was observed in the other scales (Table 4).

Discussion

In a series of 53 patients by Goh et al. (4) comparing SG and TG, no significant difference was observed in functional scales and global health status between TG and SG. However, dysphagia and eating restrictions were observed to be significantly worse in the TG group. In the conclusion of their study, they stated that there was no difference in overall QoL between patients with TG or SG, but eating restrictions and dysphagia were worse after TG (4).

According to a study of 103 cases by Rausei et al. (5), QoL showed a negative correlation with tumor stage and TG. They found that a larger resection, especially in advanced-stage cancers, led to a worse QoL. They showed that TG was associated with upper gastrointestinal tract complaints. Furthermore, patients with Billroth II reconstruction were compared with Roux-en-Y, and a lower incidence of dumping syndrome was observed with Roux-en-Y. In the conclusion, they state that QoL after gastric cancer surgery is affected by tumor and treatment-related factors. They suggest that subtotal resection should be preferred to improve patients' QoL, and Roux-en-Y should be the reconstruction of choice (5).

In the study conducted by Brenkman et al. (6), 222 patients answered questionnaires, and the results showed that deterioration occured in the functional and symptom scales of patients after gastrectomy, but they later recovered and lived with a mild level of QoL impairment. They stated that distal gastrectomy, neoadjuvant treatment, and minimally invasive gastrectomy options could be beneficial for QoL (6).

Park et al. (7) investigated the effects of patients' body mass index (BMI) on QoL. For this study, 276 patients were grouped according to their BMI values in pre- and post-operative follow-ups, and both pre- and post-operative EORTC QLQ 30 and EORTC STO22 questionnaires were completed. As a result, significantly different QoL values were found in patients due to BMI loss after TG. To reduce the deterioration in QoL, intensive nutritional support and the restoration of dietary behaviors should be implemented. Appropriate clinical and institutional approaches, as well as active medical interventions, are required to maintain patients' postoperative BMI (7).

Park et al. (8) followed 275 patients for 3 years, and pre- and post-operative QoL was measured. The result showed that the overall QoL of patients who underwent gastrectomy was highly related to their satisfaction levels regarding physical functions. The satisfaction level of patients who underwent TG, despite an early deterioration within the

first few months after surgery, later recovered and began to be as good as patients who underwent SG. Adequate preoperative counseling followed by postoperative symptomatic treatment in patients undergoing TG is the most rational and evidence-based approach to reduce QoL impairment (8).

Similarly, contemporary multi-center studies on gastric cancer patients emphasize the critical importance of preserving these physical function scores during the postoperative follow-up period (9). The reliability and cross-cultural validity of these specific QoL modules have been comprehensively re-affirmed in extensive global cohorts under updated treatment guidelines (10).

When we examine the demographic data in our study, it was observed that patients who underwent SG were younger (56.9). We see this for two reasons: first, the early detection of patients, and second, the early onset of obstructive symptoms due to the tumor being confined to the antropyloric region. The number of male patients was 59, constituting 69.9%. This rate is similar to those in other studies. In 34 (94.4%) of the SG patients, the tumor was in the antropyloric region, while 8 were in the corpus. SG was applied to tumors in the corpus as they were in the distal region. Fifteen of the total gastrectomies were in the cardia, and 26 were in the corpus. As seen, TG was applied instead of proximal gastrectomy for tumors located in the cardia. The reason for this may be the deterioration in the QoL of patients after proximal gastrectomy. D2 dissection was applied to 77 (90.6%) of the patients. According to the pathology results of the gastrectomy materials, 42 (49.7%) of the patients were at Stage 3. The tumors of 63 (74.1%) of the patients were reported as adenocarcinoma, 18 (21.2%) as signet ring cell carcinoma, and 4 (4.7%) as mixed cell carcinoma.

Looking at the QoL scale results in our study, of the parameters in the functional scale subgroup, QL (global QoL) and physical functioning were found to be higher in SG group. Role functioning, emotional functioning, cognitive functioning, and social functioning scores were higher in TG group. The reason for these differences might be that patients who underwent TG may perceive a lower risk of recurrence since the entire stomach was removed. Similarly, the remaining part of the stomach in SG might cause patients to contemplate the possibility of recurrence, but the lack of physical organ absence may make them feel better physically. Looking at the symptom scales, nausea and vomiting were observed to be more frequent in SG, while all other symptoms were seen more frequently in TG. Also on this scale, DI was found to be significantly higher in TG. When the EORTC STO22 test was examined, dysphagia was observed to be significantly higher in TG. No significant difference was observed in the other parameters.

When evaluating cancer treatment, postoperative QoL is widely accepted as an increasingly important outcome of surgical procedures, reaching the same level as mortality and survival. The limited life expectancy of patients with gastric carcinoma further increases the importance of QoL. QoL information allows patients and clinicians to make more informed preoperative decisions and also to improve patient care and symptom management.

Study Limitations

1. Design and Generalizability

Retrospective and single-center: The study design is retrospective and relies solely on data from a single institution. This introduces potential biases and restricts the generalizability (external validity) of the findings to wider patient populations.

Small sample size: The relatively small sample size limits the statistical power, especially for subgroup analyses concerning specific or rare postgastrectomy syndrome components.

2. QoL Measurement

Subjectivity of QoL data: QoL is an inherently subjective patient-reported outcome. Scores may be influenced by transient psychological factors, which limits their absolute correlation with objective clinical data.

Response burden: Using comprehensive QoL questionnaires (e.g., EORTC) may lead to response fatigue, potentially compromising data quality, particularly in elderly patients.

3. Follow-up Limitation

Limited long-term follow-up: The follow-up period may not be long enough to fully capture the patient's maximal adaptation or the late-stage effects of cancer recurrence on overall QoL.

Conclusion

Similar data were obtained when comparing the results of our study with other studies conducted on QoL. DI and dysphagia (swallowing difficulty) problems were found to be significantly higher in patients who underwent TG. These symptoms can severely affect the patient's QoL, especially in the early stages.

In light of all these results, distal SG may be preferred as it does not cause a significant impairment in the QoL, provided that the surgical procedures comply with oncological requirements.

Ethics

Ethics Committee Approval: The study protocol was reviewed and approved by the Bezmialem University Non-Interventional Ethics Committee on 10.07.2018, with the decision number

15/183.

Informed Consent: Informed consent was obtained from all participants prior to their inclusion in the study.

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Footnotes

Authorship Contributions

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

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Original Article

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Sex Estimation Based on Paranasal Sinus Dimensions: A CT Study in Turkish Adults

Paranazal Sinüs Boyutlarıyla Cinsiyet Tayini: Yetişkin Türk Popülasyonu Örneğinde BT Çalışması

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ABSTRACT

Objective: This study investigates sex differences by assessing the frontal sinus (FS), maxillary sinus (MS), and sphenoid sinuses (SS) on paranasal sinus computed tomography (CT) images to evaluate their comparative discriminatory power for sex estimation.

Methods: A total of 419 individuals (206 males and 213 females) aged 20-49 years who underwent paranasal sinus CT were retrospectively included in the study. Linear measurements of the FS (height, width, depth, and the distance between the most superior points), MS (height, width, depth, anteroposterior width at the midpoint, and the intermedial wall distance), and sphenoid sinus (height, width, depth) were obtained. Statistical analyses were performed using R software. Intra- and interobserver reliability were assessed using intraclass correlation coefficients. Descriptive statistics were calculated for all variables. The discriminatory power of each measurement for sex estimation was evaluated using receiver operating characteristic curve analysis. Additionally, multivariate logistic regression analysis incorporating all parameters was conducted to assess their combined predictive value. A significance threshold of $p<0.05$ was applied for all analyses.

Results: Of the 22 paranasal sinus dimensions measured, 19 were larger in males than in females. The most accurate measurements were left (74%) and right FS (73%) depth. The

ÖZ

Amaç: Paranazal sinüs bilgisayarlı tomografisi (BT) görüntülerinde frontal sinüs (FS), maksillar sinüs (MS) ve sfenoid sinüs (SS) ölçümleri yapılarak cinsiyetler arası farklılıkların araştırılması, cinsiyet tayini açısından paranazal sinüs boyutlarının ayırt edicilik güçlerinin birbirleriyle karşılaştırılması amaçlanmıştır.

Yöntemler: Çalışmaya paranazal sinüs BT çekilen 20-49 yaş arası olgular dahil edilmiştir. Her bir olgunun sağ ve sol FS yüksekliği, derinliği, genişliği, her iki FS tepe noktalarının birbirine olan uzaklığı, her iki MS yüksekliği, derinliği, genişliği, orta nokta genişliği, intermaksillar mesafe, her iki SS yüksekliği, derinliği ve genişliği ölçülmüştür. Verilerin istatistiksel analizinde R yazılımı kullanılmıştır. Gözlemler ve gözlemciler arası kararlılığı test etmek için inter/intra class korelasyon testi uygulanmıştır. Tanımlayıcı istatistikler frekans, yüzde, ortalama, medyan ve standart sapma değerleri ile sunulmuştur. Cinsiyet tayininde sinüs değerlerinin her biri alıcı işletim karakteristik eğrisi analizi ile incelenmiştir. Çoklu değişkenli analizde, tüm sinüs parametreleri kullanılarak lojistik regresyon analizi yapılmıştır. Tüm testlerde istatistiksel anlamlılık olarak $p<0,05$ değeri kriter kabul edilmiştir.

Bulgular: Yirmi iki ölçümden 19'unun erkeklerde kadınlardan daha büyük olduğu görülmüştür. Cinsiyet tayininde en yüksek doğruluk oranına sahip olan ölçümler sol FS derinliği (%74) ve sağ FS derinliği (%73) olarak saptanmıştır. Lojistik regresyon

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ABSTRACT

formula derived from the logistic regression analysis of right FS depth, left FS depth, left FS width, right MS height, right MS depth, right MS width, left MS depth, left MS midpoint width, and left SS height demonstrated 76% accuracy.

Conclusion: The formula produced by multiple logistic regression analyses estimated sex with accuracy of 76%. The findings support the use of paranasal sinus dimensions can be utilized for sex estimation. National scale studies are needed.

Keywords: Forensic medicine, forensic anthropology, identification, sex estimation, paranasal sinus, computed tomography

ÖZ

sonucunda; sağ FS derinlik, sol FS derinlik, sol FS genişlik, sağ MS yükseklik, sağ MS derinlik, sağ MS genişlik, sol MS derinlik, sol MS orta noktasının genişliği ve sol SS yükseklik parametreleri kullanılarak oluşturulan formül ile %76 oranında cinsiyet tayini yapılabilmiştir.

Sonuç: Çalışmada üç paranazal sinüsün boyutları kullanılarak yapılan çoklu lojistik regresyon analizleri ile üretilen formül kullanılarak %76 oranında doğru cinsiyet tayini yapılabilmesi, paranazal sinüs boyutlarının cinsiyet tayininde kullanılabileceğini göstermiştir. Gündelik uygulamada kullanımı için konuyla ilgili çok merkezli, ulusal çapta çalışmalar gereklidir.

Anahtar Kelimeler: Adli tıp, adli antropoloji, kimliklendirme, cinsiyet tayini, paranazal sinüs, bilgisayarlı tomografi

Introduction

One of the most significant problems in creating a biological profile during the identification of human remains is that bones cannot always be found intact (1-3). The paranasal sinuses, situated in a protected region of the skull and composed of robust and compact bone, demonstrate high resistance to external forces, facilitating more accurate morphometric assessment (4-7). Computed tomography (CT) and magnetic resonance imaging are the most commonly used modalities for the evaluation of the paranasal sinuses (3-6,8,9). Due to its affordability, practicality, and accuracy, CT is considered the gold standard for morphometric measurements (3-6,10). This study aimed to assess sex-related differences in the dimensions of the frontal sinus (FS), maxillary sinus (MS), and sphenoid sinuses (SS) using paranasal sinus CT scans acquired for clinical purposes between 2019 and 2022, and to compare the discriminatory potential of these parameters in sex estimation.

Methods

Permission to use the data was obtained from the chief physician, and ethical approval was granted by the Clinical Research Ethics Committee of Bolu Abant İzzet Baysal University (approval number: 2022/224, date: 09.08.2022). This study was carried out in compliance with the ethical principles outlined in the Declaration of Helsinki as revised in 2024.

Paranasal sinus CT scans of patients aged 20-49 years who were admitted to the hospital between January 1, 2019, and September 20, 2022, were retrospectively analyzed. All images were obtained using a multi-detector CT scanner (Revolution EVO, GE Healthcare, Waukesha, WI, USA). The images were acquired in a high-resolution bone window with a slice thickness of 1.25 mm, a reconstruction interval of 0.625 mm, a pitch value of 0.984, and a gantry rotation time of 0.6 s, at 100 kVp and 80 mA, with an exposure time of 2.8 s. The DICOM images were reviewed on a computer equipped with an Intel® Core™ i5-9400 CPU @ 2.90 GHz, 8.00 GB RAM, 64-bit x64-based processor, using a 1920×1080 resolution monitor and Kardelen PACS Viewer software (v.3.1.9.316). Observers were allowed to magnify the CT images and adjust image contrast and screen brightness during the measurements. Patients with a history of trauma, surgery, congenital or acquired facial anomalies, paranasal sinus pathology (e.g., acute or chronic inflammation, infection, bleeding, wall thickening, tumors), or any condition affecting bone density were excluded from the study. The height, width, depth of the FS were measured in accordance with the methods described by Akhlaghi et al. (11) and Sherif et al. (12). The distance between the most superior points of the FSs was measured following the protocol reported by Chowdhuri et al. (8) (Figure 1). Measurements of the MS, including the height, width, depth, the anteroposterior width at the midpoint, and the distance between the medial walls, were performed as described by Sherif et al. (12) (Figure 2). The height, width, and depth of both SSs were measured according to the methodology outlined by Ramos et al. (3) (Figure 3).

Statistical Analysis

Fifteen days after the initial measurement by the first operator, 25 randomly selected subjects were measured again by the same operator. The same 25 subjects were also measured twice, 15 days apart, by a second operator. To reduce bias in the results, the intraclass correlation coefficient (ICC) was computed to assess inter-intraobserver consistency.

Statistical analyses were conducted using R version 4.2.2 (2022) (R Core Team, R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria; available at https://www.R-project.org). Data for continuous variables are expressed as mean ± standard deviation, while categorical data are

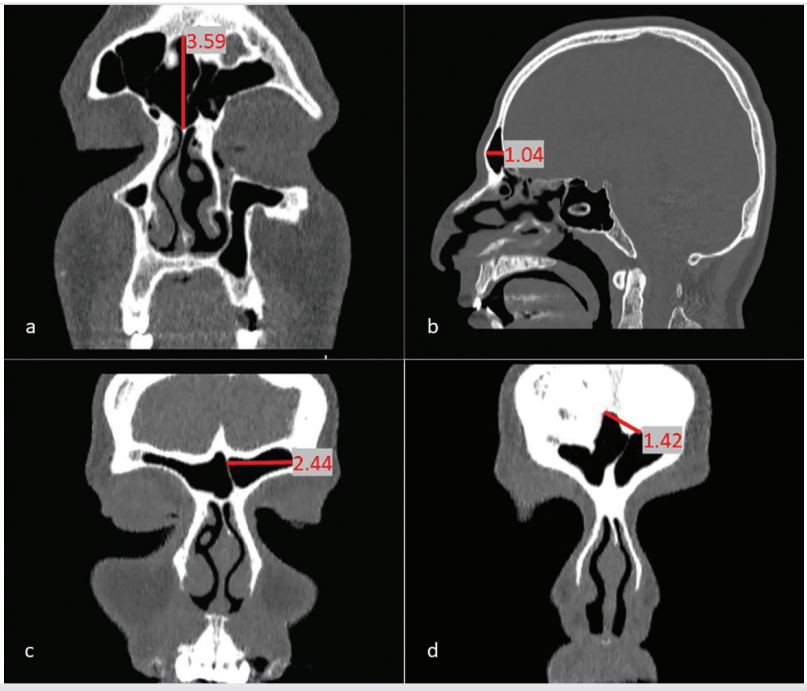

Figure 1. Measurements of frontal sinus (FS). a) FS height measurement, b) FS depth measurement, c) FS width measurement, d) distance between the apex points of FS

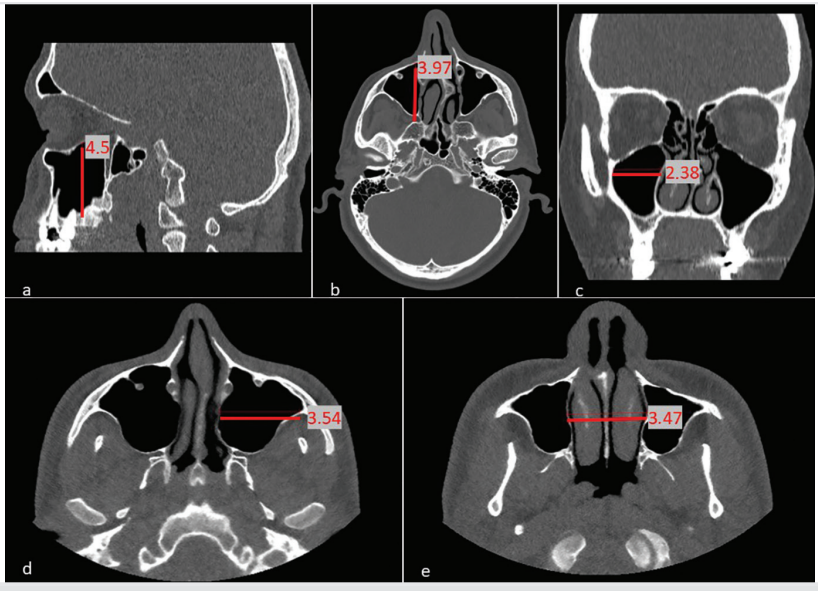

Figure 2. Measurements of maxillary sinus (MS). a) MS height, b) MS depth, c) MS width, d) width at the midpoint of the MS, e) distance between the medial walls of both MS

expressed as frequencies and percentages. Normality was evaluated both visually, with histograms, and analytically, with the Shapiro-Wilk and Kolmogorov-Smirnov tests. For normally distributed data, parametric tests were employed, and for non-normally distributed data, non-parametric tests were used. Differences between sexes were assessed using the Mann-Whitney U test. Receiver operating characteristic (ROC) curve analysis was used for each sinus measurement in sex estimation, with calculation of specificity, sensitivity, cut-off value, positive and negative predictive values, and accuracy. Logistic regression was performed with all sinus parameters; non-significant variables were removed stepwise until significant independent predictors were identified. Model fit was assessed by the Hosmer-Lemeshow test. A significance threshold of $p<0.05$ was adopted for all analyses.

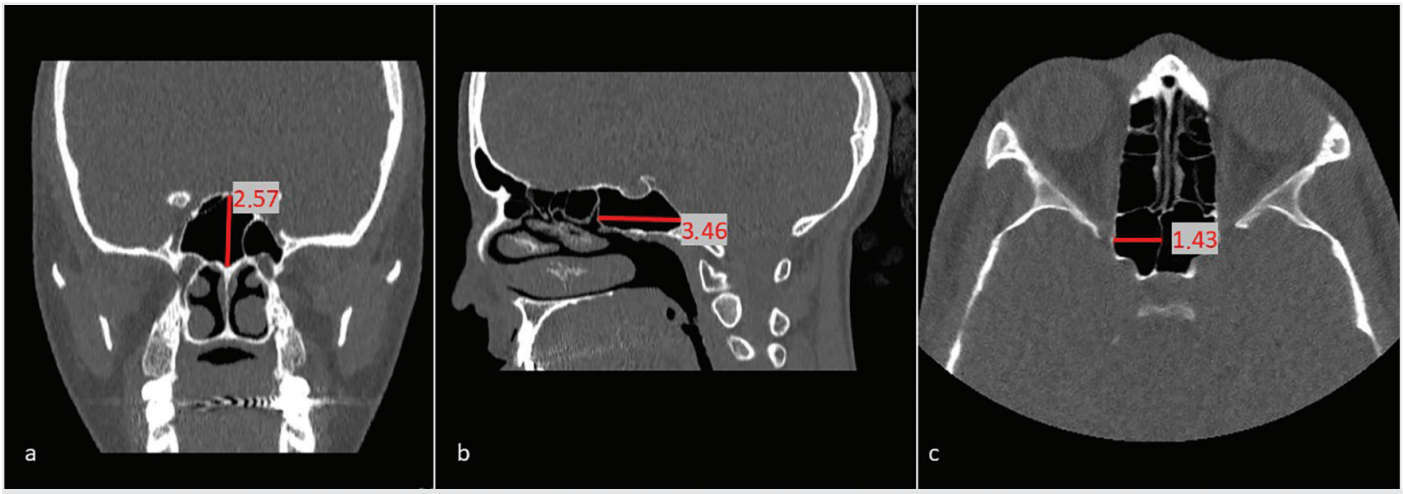

Figure 3. Measurements of sphenoid sinus (SS). a) SS height, b) SS depth, c) SS width

Results

The study included 206 male and 213 female subjects. The mean age was 30.85±9.06 years for males (min: 20, max: 49) and 32.84±8.74 years for females (min: 20, max: 49). The ICC in this study ranged from 0.99 to 1.00 (p<0.0001).

All measurements, except the left maxillary midpoint, the right SS depth and width, were larger in males. A comparison of sinus dimensions by sex is presented in Table 1.

The sensitivity, specificity, positive predictive value, negative predictive value, cut-off value, and accuracy for sex estimation were calculated (Table 2), and ROC curves were

Table 1. Comparison of sinus sizes by sex (all measurements are in cm)

	Male			Female			p-value
	Median	25th percentile	75th percentile	Median	25th percentile	75th percentile	
Right FS height	2.73	2.33	3.31	2.27	1.76	3.04	<0.001
Right FS depth	1.35	1.14	1.64	1.00	0.84	1.22	<0.001
Right FS width	3.11	2.48	3.68	2.69	1.90	3.32	<0.001
Left FS height	2.94	2.40	3.55	2.39	1.88	2.93	<0.001
Left FS depth	1.39	1.15	1.64	1.03	0.86	1.23	<0.001
Left FS width	3.25	2.58	3.77	2.81	2.22	3.41	<0.001
FS peaks distance	1.74	1.28	2.3	1.55	1.09	2.07	<0.01
Right MS height	4.26	3.82	4.60	3.96	3.51	4.20	<0.001
Right MS depth	4.01	3.79	4.26	3.96	3.67	4.16	<0.05
Right MS width	2.86	2.46	3.16	2.63	2.30	2.95	<0.001
Right MS midpoint width	2.57	2.15	2.89	2.42	2.12	2.66	<0.01
Left MS height	4.13	3.81	4.54	3.92	3.53	4.23	<0.001
Left MS depth	4.02	3.75	4.21	3.92	3.70	4.12	<0.01
Left MS width	2.78	2.38	3.17	2.67	2.37	2.96	<0.05
Left MS midpoint width	2.47	2.09	2.80	2.38	2.10	2.70	0.275
Intermaxillary distance	3.48	3.25	3.73	3.37	3.41	3.65	<0.01
Right SS height	2.34	2.06	2.57	2.09	1.78	2.36	<0.001
Right SS depth	2.77	2.19	3.24	2.68	1.97	3.17	0.080
Right SS width	2.01	1.60	2.43	1.88	1.55	2.47	0.167
Left SS height	2.30	2.04	2.62	2.03	1.79	2.28	<0.001
Left SS depth	2.88	2.30	3.24	2.54	2.03	3.12	<0.001
Left SS width	2.06	1.69	2.59	1.81	1.51	2.28	<0.001

FS: Frontal sinus, MS: Maxillary sinus, SS: Sphenoid sinus

Table 2. Sensitivity, specificity, positive/negative predictive values, accuracy, and AUC values of sinus measurements in estimating sex

	Sex prediction								
	Female (n=213)	Male (n=206)	Sensitivity	Specificity	Cut-off	PPV	NPV	Accuracy	AUC (95% CI)
Right FS height	109	160	77.6%	51.2%	2.13	60.6%	70.3%	64.2%	0.64 (0.59-0.69)
Right FS depth	156	151	73.3%	73.2%	1.17	73.2%	73.9%	73.2%	0.77 (0.72-0.82)
Right FS width	107	143	69.4%	50.2%	2.70	57.4%	62.9%	59.6%	0.63 (0.58-0.69)
Left FS height	125	145	70.3%	58.6%	2.56	62.2%	67.2%	64.4%	0.66 (0.61-0.72)
Left FS depth	157	151	73.3%	73.7%	1.18	72.9%	74.0%	73.5%	0.77 (0.73-0.82)
Left FS width	148	107	51.9%	69.4%	3.23	62.2%	59.9%	60.9%	0.63 (0.57-0.68)
FS peaks distance	94	151	73.3%	44.1%	1.39	55.9%	63.1%	58.5%	0.58 (0.52-0.63)
Right MS height	165	106	51.5%	77.5%	4.24	68.8%	62.3%	64.7%	0.67 (0.62-0.72)
Right MS depth	166	69	33.3%	77.9%	4.19	59.4%	54.8%	56.1%	0.57 (0.51-0.62)
Right MS width	178	78	37.9%	83.5%	3.04	69.0%	58.2%	61.1%	0.62 (0.57-0.68)
Right MS midpoint width	169	83	40.0%	79.3%	2.71	65.3%	57.8%	60.1%	0.57 (0.52-0.63)
Left MS height	124	133	64.6%	58.2%	4.00	59.9%	62.9%	61.3%	0.65 (0.60-0.70)
Left MS depth	120	125	60.6%	56.3%	3.97	57.3%	59.7%	58.5%	0.58 (0.53-0.64)
Left MS width	195	50	24.3%	91.5%	3.18	73.5%	55.5%	58.5%	0.56 (0.50-0.61)
Left MS midpoint width	149	83	40.3%	70%	2.62	56.5%	54.8%	55.4%	0.53 (0.47-0.58)
Intermaxillary distance	53	183	88.8%	24.9%	3.15	53.4%	69.7%	56.3%	0.57 (0.52-0.63)
Right SS height	150	119	57.7%	70.4%	2.29	65.3%	63.3%	64.2%	0.65 (0.60-0.70)
Right SS depth	58	170	82.5%	27.2%	2.03	52.3%	61.7%	54.4%	0.55 (0.49-0.60)
Right SS width	88	142	68.9%	41.3%	1.74	53.1%	57.8%	54.9%	0.54 (0.48-0.59)
Left SS height	160	110	53.4%	75.1%	2.29	67.4%	62.5%	64.4%	0.68 (0.63-0.74)
Left SS depth	138	109	52.9%	64.8%	2.84	59.2%	58.7%	58.9%	0.60 (0.47-0.65)
Left SS width	121	131	63.6%	56.8%	1.89	58.7%	61.7%	60.1%	0.60 (0.55-0.66)

FS: Frontal sinus, MS: Maxillary sinus, SS: Sphenoid sinus, AUC: Area under the curve, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value

generated. The left FS depth (74%), right FS depth (73%), and the right MS height (65%) were the measurements with the highest accuracy (Figure 4).

To determine the suitability of paranasal sinus measurements for sex estimation, logistic regression analysis was performed. The analysis identified the following parameters as significant predictors: right FS depth, left FS depth, left FS width, right MS height, right MS depth, right MS width, left MS depth, width of anteroposterior midpoint of left MS, and left SS height (Table 3). The dependent variable was coded as male=0 and female=1. The fitted model estimated the probability of being female and was expressed as:

logit[P(female)]=8.557 +(-1.115 x right FS depth)+(-2.155 x left FS depth)+(0.549 x left FS width)+(-1.132 x right MS height)+(1.947 x right MS depth)+(-1.08 x right MS width)+(-1.723 x left MS depth)+(1.626 x left MS midpoint width)+(-1.636 x left SS height).

The predicted probability of being female was calculated as P(female)=exp(logit)/[1 + exp(logit)]. A predicted probability ≥0.50 was classified as female, whereas a predicted probability <0.50 was classified as male. The discriminatory performance of the logistic regression model was assessed using ROC curve analysis. The model demonstrated good discriminative ability, with an area under the curve of 0.84 (95% confidence interval: 0.81-0.88).

Using this formula, males were predicted with 72% accuracy, females with 80% accuracy, and the overall accuracy was 76% (Table 4).

Discussion

Numerous studies have demonstrated the potential of FSs for identification (8,10,13,14). Consistent with these, this study found all FS measurements to be greater in males. Research from the Czech Republic and Egypt, along with Chalkoo et al. (9), corroborates that FS dimensions are larger in males (10,14).

In this study, the height, depth, and width of both MS, as well as the width of anteroposterior midpoint of left MS and the distance between medial walls of MS, were found to be greater in males. These findings support previous studies

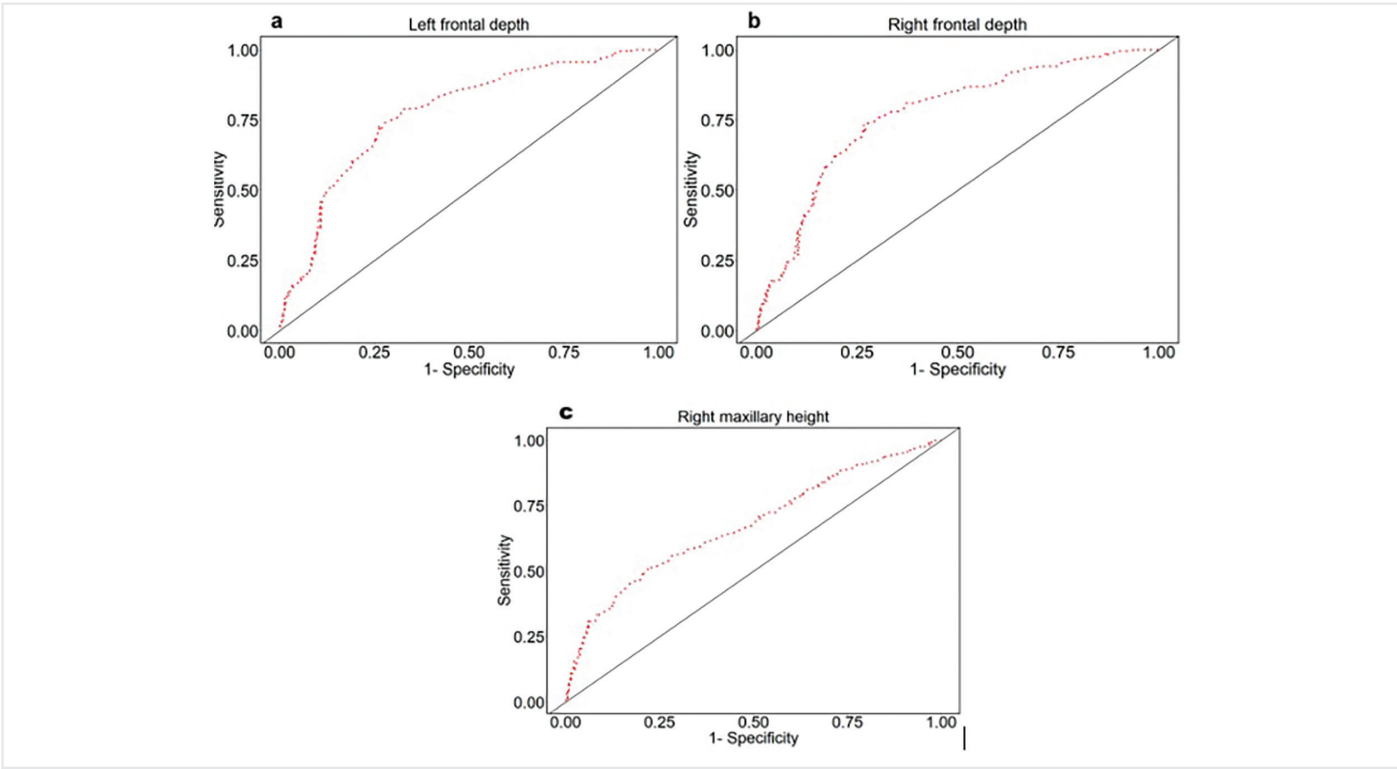

Figure 4. ROC curves of a) left FS depth, b) right FS depth, c) right MS height
ROC: Receiver operating characteristic, FS: Frontal sinus, MS: Maxillary sinus

Table 3. OR and consequences of logistic regression analysis

Measures	OR (95% CI)	p-value
Right FS depth	0.33 (0.12-0.86)	0.024
Left FS depth	0.11 (0.03-0.40)	0.001
Left FS width	1.73 (1.20-2.49)	0.003
Right MS height	0.32 (0.17-0.58)	<0.001
Right MS depth	7.01 (1.94-25.31)	0.003
Right MS width	0.34 (0.13-0.83)	0.019
Left MS depth	0.17 (0.05-0.61)	0.006
Left MS midpoint width	5.08 (2.25-11.45)	<0.001
Left SS height	0.19 (0.10-0.36)	<0.001

FS: Frontal sinus, MS: Maxillary sinus, SS: Sphenoid sinus, OR: Odds ratio, CI: Confidence interval

Table 4. Comparison of the predicted sexes with the formula and the actual sexes

		Predicted group		
		Male, n (%)	Female, n (%)	Total
Original group	Male	148 (71.8%)	58 (28.2%)	206 (100%)
	Female	43 (20.2%)	170 (79.8%)	213 (100%)
Overall percentage of male + female		318 (75.9%)		

on MSs conducted in various populations, including those by De Mendonça et al. (13), Teixeira et al. (14), Ekizoglu et al. (15), and studies from Egypt (16), Sri Lanka (17), Brazil (18), and India (19-21).

The height, depth, and width of left SS, as well as the height of right SS, were significantly greater in males; however, no sex difference was found in the depth and width of right SS. In their study, Sherif et al. (12) reported that right SS depth and width measurements were greater in males, while Ramos et al. (3) found SS volume to be greater in males, with no differences in other measurements. The weak sex differences observed in SSs may be attributed to anatomical variation and ethnic diversity.

In this study, right and left FS depths were found to be the parameters with the highest accuracy (74% and 73%) in sex estimation. In a study of 100 cases in Egypt, right FS depth was found to be the most discriminatory measurement (22), while in the study of Akhlaghi et al. (11), left FS height and in Chalkoo et al. (9), left FS depth and width were reported as the strongest sex-discriminatory parameters.

The logistic regression formula obtained in this study yielded 72% accuracy in males, 80% in females, and 76% overall. Sherif et al. (12) achieved 77% accuracy with all three sinus measurements, while Ibrahim et al. (16) achieved 72% accuracy with FS measurements, Ekizoglu

et al. (15) achieved 77% accuracy with MS measurements, and Teixeira et al. (14) achieved 74% accuracy with MS measurements. The results support the use of all three paranasal sinus measurements in sex estimation.

Study Limitations

The generalizability of this study is limited by its retrospective design and single-center nature, which reduce population diversity. It is important to consider that anthropological measurements may vary across different ethnic groups. However, our sample size is larger than those of similar studies.

As the study was designed retrospectively, reliable data on stature and other body measurements of the cases were unavailable, it was also not possible to evaluate the measured cases in terms of body dimensions. Another limitation of this study is that the logistic regression model was built and tested using the same study population. Although the model showed good discriminative ability, there was no independent external validation cohort available. Consequently, the reported classification performance might overstate the model's generalisability, and the proposed equation should be externally validated in larger, independent populations before it is adopted routinely in forensic practice.

Conclusion

The findings showed that males exhibited larger values in 19 of the 22 paranasal sinus measurements. Using a formula generated by multiple logistic regression analysis that incorporated dimensions from all three paranasal sinuses, sex determination was achieved with 76% accuracy. These results are consistent with the literature and suggest that paranasal sinus dimensions can aid sex determination in cases where other methods are inconclusive. Future national multicenter studies may facilitate the practical application of paranasal sinus measurements in forensic identification.

Ethics

Ethics Committee Approval: Ethical approval was granted by the Clinical Research Ethics Committee of Bolu Abant İzzet Baysal University (approval number: 2022/224, date: 09.08.2022).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.K.Y., M.H., Concept: B.K.Y., E.H., Design: B.K.Y., E.H., Z.Z.E., Data Collection or Processing: B.K.Y., M.H., Analysis or Interpretation: B.K.Y., E.H., Z.Z.E., S.A.K., Literature Search: B.K.Y., Writing: B.K.Y., E.H.

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

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Original Article

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Bezmialem Science 2026;14(3):285-293

The Relationship Between Preoperative Care Dependence and Postoperative Comfort Level in Patients with Hip Replacement

Kalça Protezi Olan Hastalarda Ameliyat Öncesi Bakım Bağımlılığı ile Ameliyat Sonrası Konfor Düzeyi Arasındaki İlişki

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ABSTRACT

Objective: Assessment of an individuals' need for care in the preoperative period and implementation of structured care supported by evidence-based practices are important to improve patient comfort in the postoperative period. The present study investigated how preoperative care dependency is associated with postoperative comfort in patients undergoing hip replacement surgery.

Methods: A descriptive correlational study was carried out with 120 patients at a training and research hospital in Türkiye between July 2021 and April 2022. Data were collected using an "Information Form", the "Care Dependency Scale", and the "Post Hip Replacement Comfort Scale".

Results: The patients' mean age was 68.56±14.75 years, and 72.5% (n=87) were female. The patients' mean scale scores of "Care Dependency Scale" and "Post Hip Replacement Comfort Scale" were 66.16±17.48 and 3.51±0.50, respectively. A weak yet statistically significant positive relationship was found between the scales (r=0.339, p<0.001), indicating that lower preoperative care dependency was associated with higher postoperative comfort.

ÖZ

Amaç: Ameliyat öncesi dönemde bireylerin bakım gereksinimlerinin değerlendirilmesi ve kanıta dayalı uygulamalarla desteklenen yapılandırılmış bakımın uygulanması, ameliyat sonrası dönemde hasta konforunu artırmak için önemlidir. Bu çalışma, kalça protezi ameliyatı geçiren hastalarda ameliyat öncesi bakım bağımlılığı ile ameliyat sonrası konfor arasındaki ilişkiyi incelemeyi amaçlamaktadır.

Yöntemler: Bu tanımlayıcı ve ilişki arayıcı çalışma, Temmuz 2021 ile Nisan 2022 tarihleri arasında Türkiye'deki bir eğitim ve araştırma hastanesinde 120 hasta ile yürütülmüştür. Veriler Bilgi Formu, Bakım Bağımlılığı Ölçeği ve Kalça Protezi Sonrası Konfor Ölçeği kullanılarak toplanmıştır.

Bulgular: Hastaların yaş ortalaması 68,56±14,75 yıl ve %72,5'i (n=87) kadındı. Bakım Bağımlılığı Ölçeği ve Kalça Protezi Sonrası Konfor Ölçeği toplam puan ortalamaları sırasıyla 66,16±17,48 ve 3,51±0,50 idi. Bakım Bağımlılığı Ölçeği ve Kalça Protezi Sonrası Konfor Ölçeği puanları arasında istatistiksel olarak anlamlı ve pozitif yönde zayıf bir ilişki bulundu (r=0,339, p<0,001). Bu ilişki, ameliyat öncesi daha düşük bakım bağımlılığının ameliyat sonrası daha yüksek konforla ilişkili olduğunu göstermektedir.

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ABSTRACT

Conclusion: Evaluating patients' care needs during the preoperative period may support postoperative comfort. These findings underscore the importance of tailored nursing interventions to address preoperative care dependency.

Keywords: Patient comfort, perioperative care, perioperative nursing

ÖZ

Sonuç: Ameliyat öncesi dönemde hastaların bakım ihtiyaçlarının değerlendirilmesi ameliyat sonrası konforu destekleyebilir. Bu bulgular, ameliyat öncesi bakım bağımlılığını ele almak için kişiye özel hemşirelik girişimlerinin önemini vurgulamaktadır.

Anahtar Kelimeler: Hasta konforu, perioperatif bakım, perioperatif hemşirelik

Introduction

Hip replacement surgery involves removing of the head of the femur and the acetabulum, and replacing them with artificial parts. Hip replacement surgery is indicated for a variety of conditions, primarily fractures of the femur and acetabulum, as well as primary and secondary osteoarthritis, avascular necrosis, ankylosing spondylitis, tumors, and congenital hip dislocation. The aim is to relieve the patient's pain and improve hip joint mobility (1). It is a major surgical procedure with a high risk of complications during both the preoperative and postoperative periods (2).

Determining an individual's care needs before and after surgery is critical to care management. The primary goal is to help the individual regain their ability to care for themselves independently (3). Patients who are dependent on others for care require more caregivers than independent patients. Therefore, it is crucial to determine the care needs and level of dependency of the individuals for whom nurses are responsible to improve the quality of nursing care. Moreover, knowledge of patients' care needs is fundamental to planning and managing nursing care. When determining these needs, the level of care dependency of patients is an important indicator (4).

Patients' care needs before hip replacement surgery are primarily related to mobility restrictions and extend to the entire perioperative period (1). Patients are often faced with physiological problems such as decreased appetite, pressure injuries, constipation, and orthostatic hypotension due to limited mobility. They may also experience psychological problems. These include delirium, anxiety, depression, and sleep disturbances. Social problems may also arise, such as distancing oneself from family and surroundings, and alterations in role functioning (5). This has a negative impact on patients' well-being (6).

The concept of comfort was first defined by nursing theorist Kolcaba (7) in 1991. In nursing care, comfort means attending to a patient's needs. Providing patient comfort accelerates healing and improves patient care outcomes (7). During surgery, especially in the postoperative period, patient comfort is primarily affected by postoperative pain. However, comfort is also influenced by environmental factors, such as temperature, light, and noise in the hospital setting; sociocultural factors including effective communication and patient education; and psychospiritual factors such as self-concept, sexuality, and self-awareness (8). In addition, comfort can be affected by many factors during the preoperative, intraoperative, and postoperative periods (9). These preoperative factors can affect the patient comfort during the postoperative period. These factors include the patient's physiological and psychological readiness for surgery, their fear of anaesthesia and surgery, the effectiveness of preoperative education, and their dependence on nursing care due to preoperative illness or disability (8).

Nurses care for patients with varying levels of dependency. It is crucial to assess patients' level of dependency in order to determine their nursing care needs, plan nursing interventions, assist in improving their abilities, and develop appropriate discharge plans. This ensures patient's comfort (10,11). It is expected that the pre-existing dependency on care resulting from the current illness or disability will decrease as the postoperative recovery process progresses. Consequently, an improvement in patient comfort is expected as dependency decreases. No prior research was identified exploring how preoperative care dependency relates to postoperative comfort in hip replacement patients. For this reason, the present study was conducted to evaluate that relationship.

Methods

Design and Sample

A descriptive correlational study was carried out with 120 patients at an orthopaedics and traumatology clinic of a training and research hospital in Türkiye between July 2021 and April 2022. An a priori power analysis was conducted using G*Power 3.1 with a two-tailed test, a significance level of $\alpha=0.05$, and a statistical power of $1-\beta=0.80$. Based on these assumptions and a medium effect size, the required minimum sample size was calculated as 115 participants. A non-probability, consecutive sampling method was used. Patients who met the inclusion criteria and were admitted to the orthopaedics and traumatology clinic during the data collection period were invited to participate in the study, and those who volunteered were included. Inclusion criteria were as follows: individuals who had to have undergone hip

replacement surgery, aged between 18 and 95 years, had no psychiatric illness or learning disability, had no hearing or vision problems, were cognitively able, spoke and could read Turkish, and expressed their willingness to participate in the study. This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement.

Preoperative Patient Information

In the study setting, all patients scheduled for hip replacement surgery routinely received standardized preoperative information as part of usual care. This information was provided by the responsible nurse and/or physician during the preoperative hospitalization period and included explanations about the surgical procedure, anaesthesia, postoperative pain management, early mobilization, use of assistive devices, and basic self-care activities. The information was delivered verbally and supported by routine written materials when available. No additional or study-specific educational intervention was implemented as part of this research.

Data Collection Tools

Patients were seen in the service one day before and two days after the surgery. The "Information Form" and the "Care Dependency Scale" (CDS) were completed the day before surgery, and the "Post Hip Replacement Comfort Scale" (PHRCS) was completed on the second day after surgery. The form took about 15 minutes to complete.

Information Form: It contains a total of 18 questions covering demographics (e.g., age, gender, marital status, body mass index, employment status, education level, presence of chronic diseases, smoking and alcohol consumption habits, use of assistive devices such as walkers or canes, and previous surgeries) and perioperative characteristics (e.g., reason for surgery, previous hip replacement surgeries, and type of surgery, anaesthesia, and analgesia). The form was developed by the researchers based on a review of the relevant literature and routine clinical assessment practices in orthopaedic and perioperative care. The patients' pain levels were assessed using the "Visual Analogue Scale", in which they marked a point on a 10-cm line ranging from "no pain" to "worst pain".

CDS: This scale is based on Virginia Henderson's framework of human needs. It was developed by Dijkstra et al. (11) to assess patients' care dependency situations. The scale's validity and reliability were studied in Türkiye by Hakverdioğlu-Yönt et al. (12). It is a 5-point Likert scale consisting of 17 items covering activities of daily life. The lowest possible score is 17, and the highest possible score is 85. A high score indicates that patients can meet their care needs independently, while a low score indicates that they rely on others to do so. In the Turkish version of the scale, the Cronbach's alpha was 0.91 (12). This study found that Cronbach's alpha for the scale was 0.971.

PHRCS: Saray Kilic and Tastan (6) developed the scale for assessing patient comfort during the hospital stay after hip replacement surgery in 2017, and the scale was designed to be administered on postoperative day 2, which corresponds to the period when early postoperative recovery stabilizes and patient comfort can be reliably evaluated. Consisting of 26 items, it had a single factor and a 5-point Likert scale. The total score was divided by the number of items to obtain the average score. The highest possible average score is 5, and the lowest is 1; a higher total score indicates greater patient comfort. In the original development study, Cronbach's alpha was reported as 0.758 (6). The Cronbach's alpha for the scale was 0.846 in this study.

Statistical Analysis

The data analysis for this study was performed using SPSS-21.0 statistical software program (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). The Kolmogorov-Smirnov test was used to assess whether the data conformed to a normal distribution. For the statistical analysis of the data, descriptive methods were used. These methods included the mean, standard deviation, frequency, minimum and maximum. Due to the non-normal distribution of the data, Mann-Whitney U, Kruskal-Wallis, and Spearman correlation tests were used to evaluate links between descriptive characteristics and scale outcomes. The correlation coefficient "r" was interpreted and categorized as follows: 0-0.2=very weak, 0.2-0.4=weak, 0.4-0.6=moderate, and 0.6-0.8=strong. All statistical tests were conducted with a significance level set at $p<0.05$.

Ethical Approval

Ethics committee approval was obtained from the İstanbul Kent University Ethics Committee (approval number: 2021-05, date: 29.06.2021). Prior to the study, approval was obtained from the hospital, and written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Results

The mean age of the patients was 68.56±14.75 (min: 21, max: 94) years. Of these patients, 72.5% (n=87) were female. Of these patients, 58.3% (n=70) had fractures and 69.2% (n=83) underwent total hip replacement surgery. On the second day after surgery, the pain levels of patients were 4.85±2.44 (min: 0, max: 10), and the number of mobilizations was 1.86±1.24 (min: 0, max: 6). The other demographic and perioperative characteristics of the participants are shown in Tables 1 and 2.

The mean scale scores for patients on the CDS and the PHRCS were 66.16±17.48 (min: 19, max: 85) and 3.51±0.50 (min: 2.23, max: 4.46), respectively. There was a weak yet statistically significant positive relationship between the two scores (r=0.339) (p<0.001). As the level of patient care dependency decreases during the preoperative period, the level of postoperative comfort increases (Table 3).

Examining the relationship between certain patient characteristics and the total CDS and PHRCS scores revealed statistically significant relationship between CDS and patients' level of education (KWχ^2=9.648), marital status (Z=-2.553), and use of an assistive device (Z=-5.226) (p<0.05). It was determined that patients who were married, had a higher level of education, and did not use assistive devices had lower levels of care dependency. A statistically significant relationship was found between the PHRCS and patients' gender (Z=3.343), education level (KWχ^2=8.186), marital and employment status (Z=-4.002, Z=-2.752), chronic diseases (Z=-2.042), use of an assistive device (Z=-2.858), type of hip replacement and anaesthesia (Z=-3.690, Z=-2.265), and reason for surgery (KWχ^2=21.146) (p<0.05). Patients who were male, had a higher level of education, were employed, did not have a chronic disease and did not used assistive devices, had undergone total hip replacement surgery, and had received spinal anaesthesia reported higher postoperative comfort. There was a statistically significant and negative moderate relationship between CDS and age (r=-0.531). There was also a negative weak relationship between CDS and pain intensity on postoperative second day (r=-0.255). There was a positive moderate relationship between PHRCS and age (r=0.415), and negative moderate relationship between PHRCS and pain intensity on postoperative second day (r=-0.490) (p<0.05). Given that higher CDS scores indicate lower levels of care dependency, the negative correlation between CDS and age suggests that care dependency increases with advancing age. Similarly, the negative association between CDS and pain intensity indicates that higher care dependency is associated with increased postoperative pain. Furthermore, the negative relationship between pain intensity and PHRCS demonstrates that increased postoperative pain is associated with lower postoperative comfort levels (Table 4).

Table 1. Demographic characteristics of participants

	$\bar{X}$ ± (SD)	Min	Max
Age (years)	68.56±14.75	21	94
Body mass index (kg/m²)	28.53±4.91	15.63	41.42
		n	**%**
Gender	Female	87	72.5
	Male	33	27.5
Marital status	Married	75	62.5
	Single	45	37.5
Education level	Primary school	83	69.2
	High school	19	15.8
	University	18	15.0
Employment status	Employed	14	11.7
	Unemployed or retired	106	88.3
Chronical diseases	Yes	98	81.7
	No	22	18.3
Using an assistive device	Yes	62	51.7
	No	58	48.3
Previous surgery	Yes	90	75.0
	No	30	25.0

SD: Standard deviation

Table 2. Perioperative characteristics of participants

		n	%
Reason for surgery	Fracture	70	58.3
	Primary osteoarthritis	30	25.0
	Secondary osteoarthritis	6	5.0
	Avascular necrosis	2	1.7
	Congenital hip dislocation	12	10.0
History of hip replacement surgery	Present	20	16.7
	Absent	100	83.3
Hip replacement procedure types	Total hip replacement	83	69.2
	Partial hip replacement	37	30.8
Type of anesthesia	General	14	11.7
	Spinal	106	88.3
Type of analgesia	Epidural	18	15.0
	Patient controlled analgesia	5	4.2
	Others	97	80.8
	$\bar{X}$ ± (SD)	**Min**	**Max**
Pain intensity on postoperative day 2	4.85±2.44	0	10
Frequency of mobilization on postoperative day 2	1.86±1.24	0	6

SD: Standard deviation

Table 3. Average scores and correlations of the scales

Scales	$\bar{X}$ ± (SD)	Min-Max	r	p-value
Comfort score	3.51±0.50	2.23-4.46	**0.339**	**<0.001***
Care dependency score	66.16±17.48	19-85		

*: p<0.05 Spearman's correlation, SD: Standard deviation

Table 4. The relationship between participant characteristics and the dependency and comfort scores

		Care dependency scores		Comfort scores	
		$\bar{X}$ ± (SD)	Z_{MWU} p	$\bar{X}$ ± (SD)	Z_{MWU} p
Gender	Female	66.27±17.55	-0.168	3.41±0.50	**3.343**
	Male	65.85±17.55	0.867	3.76±0.40	**0.001***
Marital status	Married	69.96±14.39	**-2.553**	3.66±0.42	**-4.002**
	Single	59.87±20.33	**0.011***	3.26±0.53	**<0.001***
Employment status	Employed	73.43±9.87	-1.348	3.85±0.35	**-2.752**
	Unemployed	65.20±18.06	0.178	3.46±0.50	**0.006***
Chronical diseases	Yes	65.19±17.93	-1.230	3.46±0.51	**-2.042**
	No	70.45±14.93	0.219	3.71±0.37	**0.041***
Using an assistive device	Yes	59.03±17.36	**-5.226**	3.38±0.53	**-2.858**
	No	73.77±14.18	**<0.001***	3.64±0.43	**0.004***
Previous surgery	Yes	66.01±16.87	-0.790	3.53±0.49	-0.891
	No	66.60±19.50	0.430	3.43±0.53	0.373
Previous hip replacement surgery	Yes	65.00±20.24	-0.039	3.71±0.33	-1.705
	No	66.39±16.98	0.969	3.47±0.52	0.088
Type of hip replacement	Total	67.59±15.95	-0.723	3.63±0.45	**-3.690**
	Partial	62.94±20.36	0.470	3.24±0.52	**<0.001***
Type of anesthesia	General	59.36±16.76	-1.716	3.21±0.54	**-2.265**
	Spinal	67.06±17.45	0.086	3.55±0.48	**0.023***
		$\bar{X}$ ± (SD)	$KW\chi^2$ p	$\bar{X}$ ± (SD)	$KW\chi^2$ p
Education level	Primary school (a)	62.43±18.97	**9.647**	3.41±0.53	**8.186**
	High school (b)	75.42±8.99	**0.008***	3.74±0.34	**0.017***
	University (c)	73.55±9.76	**a<b,c****	3.70±0.35	**a<b****
Reason for surgery	Fracture (a)	63.17±19.93	2.787 0.594	3.34±0.53	**21.146** **<0.001*** **a<b,e****
	Primary osteoarthritis (b)	68.47±13.02		3.79±0.33	
	Secondary osteoarthritis (c)	72.17±18.13		3.45±0.37	
	Avascular necrosis (d)	75.50±0.71		3.42±0.71	
	Congenital hip dislocation (e)	73.25±7.39		3.81±0.22	
Type of analgesia	Epidural	72.94±12.83	2.563 0.278	3.58±0.39	0.483 0.785
	Patient controlled analgesia	69.60±9.55		3.61±0.49	
	Others	64.72±18.29		3.49±0.52	
		r	p	r	p
Age (years)		**-0.531**	**<0.001***	**0.415**	**<0.001***
Body mass index (kg/m²)		0.081	0.385	0.081	0.383
Pain intensity on postoperative day 2		**-0.255**	**0.005***	**-0.490**	**<0.001***
Frequency of mobilization on postoperative day 2		0.044	0.637	-0.020	0.831

*: p<0.05, **: Post-hoc analysis, Z_{MWU}: Mann-Whitney U, $KW\chi^2$: Kruskal-Wallis, r: Spearman correlation, SD: Standard deviation

Discussion

Assessing an individual's care needs and level of independence plays an important role in planning care and improving the quality of care provided. Comfort, experienced by patients as a sense of positivity and empowerment, is multidimensional. It encompasses not only the alleviation of physical discomfort, but also positive emotions such as confidence, a sense of competence and personal control, and feelings of being valued, cared for, safe, and at ease (13). Understanding the relationship between comfort and care dependency in patients undergoing orthopaedic surgery, where care dependency levels are expected to be influenced by the surgical process, may support nurses in optimizing care outcomes for patients undergoing orthopaedic surgery.

In this study, the mean total CDS score was 66.16±17.48 (min: 19, max: 85). Among literature studies using the same scale, Akyazı (14) reported a mean patient score of 40.26±12.73 for those undergoing orthopaedic surgery, while Akın Korhan et al. (15) reported a mean scale score of 73.79±18.11 for patients hospitalized in surgical clinics, and 68.45±22.77 for those hospitalized in internal clinics. Durgun et al. (16) reported a mean score of 69.12±17.80. The mean CDS score in the present study was higher than that reported by Akyazı (14), but slightly lower than those reported in some other surgical and medical patient populations (15,16). These differences may reflect variations in patient characteristics, particularly age, functional limitations, and underlying comorbidities. These patients typically experience long-standing pain, reduced mobility, and progressive functional limitations prior to surgery, which can increase their dependence on others for daily activities even before hospitalization. In addition, hip replacement candidates are often older adults with multiple comorbid conditions, further contributing to increased care needs. The chronic nature of hip pathology and the prolonged period of functional impairment before surgery may therefore result in higher perceived care dependency compared with more heterogeneous surgical populations.

In this study, the mean total PHRCS score for patients was 3.51±0.50 (min: 2.23, max: 4.46), indicating a moderate level of perceived comfort among patients on the second postoperative day following hip replacement surgery. Saray Kilic and Tastan (6), who developed the PHRCS, reported a mean score of 3.64±0.43 when evaluating the effects of nursing interventions on patient comfort. Similarly, İbrahimoğlu et al. (17) reported that the overall mean score of the PHRCS was 3.58±0.40. The similarity of these findings suggests that early postoperative comfort levels after hip replacement are relatively consistent across different settings when standard perioperative and postoperative care protocols are applied. From a clinical perspective, the moderate comfort level observed on the second postoperative day may reflect the balance between effective pain control, early mobilization efforts, and ongoing physical discomfort related to surgical trauma, movement limitations, and fatigue. Although routine postoperative nursing care—including analgesia management, mobilization support, wound care, and patient education—likely contributes positively to comfort, patients may still experience residual pain, sleep disturbance, anxiety, and functional dependence at this early stage of recovery. This suggests that while standard care may help maintain a reasonable level of comfort, there remains potential for targeted supportive strategies that may enhance symptom control and psychosocial support during the early postoperative period.

It is expected that care dependency will decrease during the postoperative recovery process, resulting in increased patient comfort. This study found a weak yet statistically significant positive correlation between the CDS and the PHRCS ($r=0.339$) ($p<0.001$). This finding suggests that patients who were more care-dependent in the preoperative period also tended to report lower levels of comfort in the early postoperative period. Previous studies examining surgical patients' comfort and its influencing factors have similarly shown that the surgical experience and recovery process have a direct impact on patients' comfort levels (18,19). Furthermore, patients hospitalized in internal medicine clinics have been reported to have higher levels of care dependency (10,15), which may be related to advanced age, prolonged hospitalization, chronic illnesses, and multiple ongoing treatments.

According to the data obtained in this study, patients with a high level of education and who did not use assistive devices had a lower dependency level on preoperative care and higher postoperative comfort level. Köberich et al. (20) stated that there was no change in patients' care dependency levels after they received self-care education. Durgun et al. (16), however, stated that care dependency decreased as the level of education increased. This finding suggests that patients with higher levels of education may be better able to understand use routine preoperative information, enabling them to take responsibility for their own care and to maintain higher levels of independence. This, in turn, may positively influence their perceptions of comfort after surgery. Similarly, patients who did not require assistive devices prior to surgery reported lower preoperative care dependency and higher postoperative comfort. İbrahimoğlu et al. (17) likewise reported that patients using assistive devices before hip replacement surgery experienced lower perceptions of perioperative care and reduced postoperative comfort. The use of assistive devices before surgery often reflects more severe hip joint deformities and functional limitations. Greater deformity may increase care dependency in the preoperative period

and may also be associated with longer surgery duration, more complex procedures, prolonged hospitalization, and a higher likelihood of revision surgery (21,22), all of which may negatively affect postoperative comfort (23). This study also found that male patients and those without chronic diseases experienced higher levels of comfort, postoperatively. Büyükünalan Şahin and Rızalar (18) similarly reported that male patients experienced higher levels of postoperative comfort than female patients, which they attributed to women's greater domestic and caregiving responsibilities. Patients without chronic diseases experience greater postoperative comfort may be explained by lower symptom burden and fewer functional limitations among patients without chronic comorbidities, which may support better comfort perceptions in the postoperative period.

Untreated pain has been shown to reduce quality of life and may lead to withdrawal from active life (24). In the present study, higher postoperative comfort levels observed among patients receiving spinal anaesthesia may be related to its effectiveness in reducing pain perception during and after surgery. In addition, pain emerged as an important factor associated with both care dependency and comfort in the early postoperative period. Given that higher scores on the CDS indicate lower levels of care dependency, the negative association observed between CDS and age suggests that care dependency increases with advancing age, while postoperative comfort levels also increased with age (Table 4). Although advancing age is generally associated with reduced functional capacity and greater dependence on others for daily activities (15,25), older patients may report higher comfort levels postoperatively due to lower activity expectations, greater acceptance of physical limitations, or more intensive caregiving support. However, chronic conditions, use of assistive devices, and delayed mobilization may increase pain and functional impairment, which in turn can negatively affect comfort. Previous studies have shown that patients with chronic pain, delayed postoperative mobilization, and poorer functional status experience lower comfort levels following hip replacement surgery (26). Although hip replacement surgery can improve preoperative functional limitations and thereby enhance long-term comfort, postoperative pain related to surgical trauma may temporarily reduce comfort during the early recovery phase (27,28). Consistent with the findings of this study, Büyükünalan Şahin and Rızalar (18), Mondanaro et al. (29), and Aydıngülü and Arslan (30) reported a significant negative association between pain and comfort in the early postoperative period, with higher pain levels being associated with lower comfort. These findings highlight the importance of effective postoperative pain management as a key strategy for improving patient comfort.

Study Limitations

This study was conducted among patients undergoing hip replacement surgery at the orthopaedics and traumatology clinic of a training and research hospital in Türkiye; therefore, the findings cannot be generalized to other surgical populations. Another limitation is that care dependency and comfort were assessed only using self-reported instruments and were not complemented by objective functional or performance-based measures. Preoperative objective assessments of dependency (such as standardized functional performance tests) were not performed because many patients were older adults with advanced hip pathology, pain, and limited mobility, and additional physical assessments in the preoperative period were considered potentially burdensome and fatiguing for this population. In addition, time constraints and routine clinical workflows in the preoperative setting limited the feasibility of conducting extensive objective assessments. As a result, the study relied on patient-reported outcomes, which may be influenced by individual perception and reporting bias. Furthermore, postoperative comfort and pain were assessed at a single postoperative time point, as defined by the original scale protocol, which may limit the ability to capture longitudinal changes during the recovery process. Additionally, although significant associations were identified, the analyses were limited to bivariate comparisons. Potential confounding factors, including age, pain severity, surgical characteristics, and assistive device use, were not adjusted for in multivariable models. Future studies using multivariable analytical approaches are warranted to better clarify the independent contribution of preoperative care dependency to postoperative comfort.

Conclusion

This study highlights the close relationship between patients' preoperative care dependency and their postoperative comfort following hip replacement surgery. The findings underscore the importance of recognizing care dependency as a relevant factor influencing patients' recovery experiences and perceived comfort. From a clinical perspective, identifying patients with higher levels of dependency before surgery may help healthcare professionals anticipate which individuals are more likely to experience lower comfort in the early postoperative period and may therefore benefit from more individualized support and follow-up. These results contribute to the growing body of knowledge on patient-centered outcomes in orthopaedic surgery and emphasize the need to integrate assessments of care dependency and comfort into routine perioperative care planning. Future studies with larger and more diverse samples are recommended to further explore these relationships and to inform the development of targeted supportive strategies that may enhance patient comfort.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the İstanbul Kent University Ethics Committee (approval number: 2021-05, date: 29.06.2021).

Informed Consent: Prior to the study, approval was obtained from the hospital, and written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Concept: Ö.İ., B.Ö., İ.K., Design: Ö.İ., B.Ö., İ.K., Ö.Ö., Data Collection or Processing: İ.K., Ö.Ö., Analysis or Interpretation: Ö.İ., B.Ö., Literature Search: Ö.İ., B.Ö., Writing: Ö.İ., B.Ö.

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Original Article

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Factors Affecting Attachment Loss in Clear Aligner Treatment: A Prospective Clinical Study

Şeffaf Plak Tedavisinde Ataçman Kaybını Etkileyen Faktörler: Prospektif Klinik Çalışma

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ABSTRACT

Objective: This study aimed to evaluate the incidence of composite attachment loss in patients undergoing clear aligner treatment and to identify patient-, tooth-, and treatment-related factors associated with attachment debonding.

Methods: Twenty-one patients (17 females, 4 males; mean age 23.86±8.21 years) receiving clear aligner therapy were included. Attachments were bonded according to the manufacturer's protocol using high-viscosity composite. Patients were followed for 6 months and attachment loss was recorded at routine appointments. Statistical analyses were performed using Fisher's exact test, Yates' correction, and Pearson chi-square test, with p≤0.05 considered significant.

Results: Among 427 attachments, 21 were lost. Attachment loss was significantly associated with attachment type (conventional vs. optimized, p=0.009) and tooth type (p=0.0005), with the highest loss rate observed in molars. No significant associations were observed between attachment loss and attachment size, dental arch, patient sex, chewing habits, daily aligner wear time, aligner removal frequency, or removal direction.

Conclusion: Attachment loss in clear aligner treatment was associated with attachment type and tooth type. Optimized attachments showed improved retention, while molars exhibited the highest attachment loss rate.

Keywords: Clear aligner therapy, orthodontic attachments, attachment loss

ÖZ

Amaç: Bu çalışmanın amacı, şeffaf plak tedavisi gören hastalarda kompozit ataçman kaybı insidansını değerlendirmek ve ataçman debondingi ile ilişkili hasta, diş ve tedaviye bağlı faktörleri belirlemektir.

Yöntemler: Şeffaf plak tedavisi gören 21 hasta (17 kadın, 4 erkek; ortalama yaş 23,86±8,21 yıl) çalışmaya dahil edildi. Ataçmanlar, üretici firmanın protokolüne uygun olarak yüksek viskoziteli kompozit kullanılarak yapıştırıldı. Hastalar 6 ay boyunca takip edildi ve rutin randevularda ataçman kayıpları kaydedildi. İstatistiksel analizler Fisher'ın kesin testi, Yates düzeltmesi ve Pearson ki-kare testi kullanılarak yapıldı; p≤0,05 değeri istatistiksel olarak anlamlı kabul edildi.

Bulgular: Toplam 427 ataçmandan 21'i kaybedildi. Ataçman kaybı, ataçman tipi (konvansiyonel ve optimize, p=0,009) ile diş tipi (p=0,0005) ile anlamlı şekilde ilişkili bulundu. Ataçman boyutu, dental ark, hastanın cinsiyeti, çiğneme alışkanlıkları, günlük plak kullanım süresi, plak çıkarma sıklığı veya çıkarma yönü ile ataçman kaybı arasında anlamlı bir ilişki saptanmadı.

Sonuç: Şeffaf plak tedavisinde ataçman kaybı, ataçman tipi ve diş tipi ile anlamlı olarak ilişkilidir. Optimize ataçmanlar daha iyi retansiyon gösterirken, en yüksek ataçman kaybı molar dişlerde gözlenmiştir.

Anahtar Kelimeler: Şeffaf plak tedavisi, ortodontik ataçmanlar, ataçman kaybı

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Introduction

Clear aligner therapy has gained widespread popularity as an alternative to conventional fixed appliances, largely due to increasing aesthetic concerns and a greater emphasis on patient comfort. Compared with traditional bracket systems, clear aligners provide superior aesthetics, improved comfort, easier maintenance of oral hygiene, reduced soft tissue irritation, and enhanced invisibility during social interactions, all of which contribute to their growing acceptance among patients and clinicians alike (1-4).

Composite attachments are bonded to tooth surfaces using templates to enhance the efficiency of tooth movement in aligner systems, making them an integral component of aligner therapy. They can be designed to aid in controlling specific tooth movements or serve as anchorage units, playing a critical role in enhancing force delivery for challenging movements such as rotation, intrusion, and extrusion, while also improving aligner retention (5). In systems such as Invisalign, attachments are generally categorized as conventional or optimized. Conventional attachments are standardized in shape, typically rectangular, whereas optimized attachments are irregular and individually designed according to tooth morphology (3). These attachments are virtually planned and bonded using dedicated templates, with different shapes serving distinct biomechanical purposes. Clinicians prescribe attachments for teeth requiring greater control to enhance the predictability of complex movements (6). Initially, ellipsoid-shaped attachments were used, but they were later replaced by bulkier conventional forms—horizontal, vertical, and beveled—to improve biomechanical control. In 2009, Align Technology introduced optimized (SmartForce®) attachments, which are automatically applied by the software under predefined criteria and are claimed to improve the efficiency of orthodontic force application for certain movements (7).

Attachment loss remains a common clinical challenge in clear aligner therapy. Although the biomechanical importance of attachments is well recognized, limited evidence exists regarding the incidence of attachment loss, the factors influencing it, and the differences among attachment types. Understanding the underlying causes of attachment loss is clinically relevant, as it directly affects treatment predictability, efficiency, and patient satisfaction. Loss of attachments during therapy can compromise outcomes by reducing movement predictability, increasing the need for additional appointments, and prolonging overall treatment duration. This highlights the need for prospective clinical studies to clarify risk factors and optimize attachment design and placement.

Therefore, the aim of this study was to evaluate the incidence of composite attachment loss in patients undergoing clear aligner treatment, to identify potential risk factors, and to contribute to the development of clinical strategies to minimize attachment loss and enhance treatment efficiency.

We hypothesize that attachment type, patient-related factors, tooth position, and treatment variables do not significantly affect attachment loss in clear aligner therapy. This hypothesis assumes that patients maintain high compliance with aligner wear and that attachments are bonded according to the recommended protocol.

Methods

Ethical Approval

The study protocol and informed consent process were conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of Bezmialem Vakıf University (approval no: 2022/19, date: 18.01.2022). Written informed consent was obtained from all participants prior to enrollment. This study was retrospectively registered at ClinicalTrials.gov (NCT07352644).

Study Design and Participants

A total of 21 patients were included. Based on a previous study (8), a sample size of 20 participants was calculated to achieve 80% power with a significance level of α=0.05 and a 95% confidence interval (CI). The participants were recruited among orthodontic patients scheduled to begin clear aligner treatment (Invisalign®, Align Technology, San Jose, CA, USA) at Bezmialem Vakıf University Department of Orthodontics between January and June 2022.

Inclusion Criteria

Permanent dentition (a), mild to moderate crowding (b), no history of previous orthodontic treatment with fixed appliances or aligners (c).

Exclusion Criteria

Poor oral health (a), bruxism (b), crown restorations (c), dental fluorosis (d), enamel hypoplasia or structural abnormalities affecting attachment bonding (e).

Patients with bruxism, identified via both self-report and clinical intra-extra oral examination, were excluded.

All patients were scanned with an intraoral scanner, and complete orthodontic documentation was obtained. Virtual treatment planning was performed using ClinCheck® software (Invisalign®), and aligners with corresponding attachment templates were fabricated (Figure 1).

Attachment Bonding Protocol

All attachments were produced with the initial template. The teeth were etched with 35% phosphoric acid (DMG Etching Jumbo Gel) for 30 seconds, rinsed with water for 30 seconds, and air-dried. A light cured bonding agent (TRULOCK® Light Activated Bonding Resin, Rocky Mountain Orthodontics,

Denver, Colorado, USA) was applied and polymerized with an LED curing unit (VALO® Cordless, Ultradent Products, Inc., South Jordan, Utah, USA). Every attachment reservoir was filled with composite in accordance with the clinical guidelines presented by Invisalign®. Each attachment reservoirs in the templates were filled with a high-viscosity composite resin (TruLock® Light Activated Adhesive). The template was seated intraorally with finger pressure, and additional pressure was applied near the attachments to ensure proper adaptation. The composite was light cured for 10 s (5 s each from the mesial and distal sides) using the same curing unit. Excess resin was removed and polished with a high-speed handpiece and white stone burs. All procedures were performed by the same department clinicians in accordance with the manufacturers' guidelines.

Patient Instructions and Follow-up

Patients were instructed to wear their aligners for 20-22 hours per day, replacing them every 10 days and to remove them before eating and drinking. Oral hygiene instructions were provided. Patients attended follow-up visits approximately every 4 weeks. Attachment loss was defined as detachment or the presence of irregular residual composite. Each patient was monitored for 6 months and data on attachment loss were documented, including the number, location, size, and type of attachment (optimized/conventional) lost (Figure 1). For each attachment, data regarding type (optimized/conventional), size, tooth type, and position in the dental arch were documented.

Additional patient-related factors such as unilateral chewing habits, type of malocclusion, number and type of attachments, use of intermaxillary elastics, frequency of aligner removal, duration of daily wear and direction of aligner removal were recorded.

Attachment Placement and Assessment

Attachments were placed following standard treatment planning protocols, with no customized designs or force-specific positioning applied. Attachment integrity was evaluated at each follow-up visit through direct intraoral examination under dental unit illumination, complemented by tactile verification using a dental explorer. An attachment was considered lost when complete or partial debonding, indicated by irregular residual composite, was observed (Figure 2).

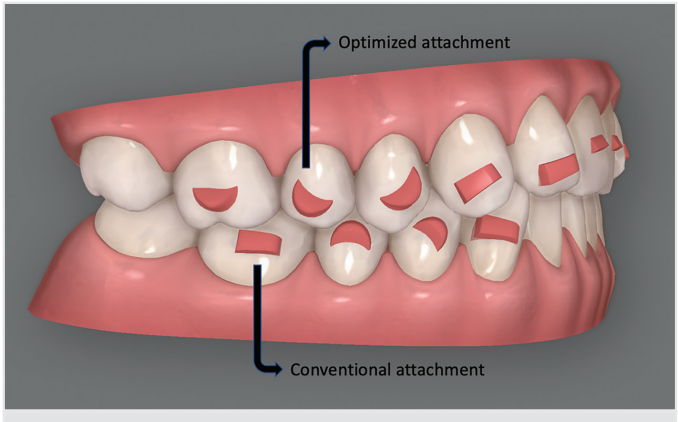

Figure 1. Optimized and conventional attachments on ClinCheck® software

All attachment loss assessments were performed by a single experienced orthodontist, minimizing inter-examiner variability. To further ensure accuracy, all recorded attachment loss events were reviewed and confirmed by the clinical director, a senior orthodontist, at each follow-up visit before any corrective procedures. No formal intra-rater reliability analysis was conducted.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Categorical variables were analyzed with Fisher's exact test when expected frequencies were <5, Yates' correction when expected values were 5-25, and Pearson's chi-square test when expected values were >25. For tables larger than 2×2, Pearson's chi-square test was applied. A p-value ≤0.05 was considered statistically significant.

Results

Twenty-six patients were initially enrolled; five were excluded due to incomplete cooperation, leaving 21 patients for analysis. The final study sample consisted of 21 patients (17 females, mean age: 23.59±8.64 years; 4 males, mean age: 25.00±6.98 years; overall mean age: 23.86±8.21 years). Attachment loss occurred in 10 patients (47.6%), with 21 of 427 attachments (4.9%) failing. The incidence of attachment loss according to patient-related factors are presented in Table 1. Attachment loss was not significantly associated with sex, daily aligner wear, removal direction or frequency, or unilateral chewing (p>0.05; Table 1).

The incidence of attachment loss according to treatment position factors are presented in Table 2. Attachment loss was not associated with the number of attachments (p=1.00), use of intermaxillary elastics (p=0.361), or size of conventional attachments (p=0.453). Attachment type was significantly associated with loss, with conventional attachments showing higher attachment loss rates than optimized attachments (p=0.009; Table 2). Attachment type was significantly associated with attachment loss in the logistic regression model, with conventional attachments exhibiting a higher risk of attachment loss than optimized attachments (odds ratio=3.73; 95% CI: 1.40-9.93; p=0.008).

The incidence of attachment loss according to tooth-related factors is presented in Table 3. No statistically significant differences were observed between attachment loss and dental arch or arch side (p>0.05). However, attachment loss differed significantly according to tooth type (p<0.001). The

highest attachment loss rate was observed in molars (10.6%), followed by premolars (4.2%) and incisors/canines (0.7%).

Discussion

Attachments used in the clear aligner treatments increase the retention of the aligners and provide better control over tooth movement (9). Attachments are crucial mechanical components; and their damage may sometimes cause the tooth to not track properly, which may affect treatment results. Attachment loss may prolong treatment duration and alter treatment prognosis, leading to significant clinical challenges. Limited data exist regarding attachment loss, and this study aimed to identify potential risk factors associated with it.

In our study 21 out of 427 attachments were lost. Previous studies report varying rates of attachment loss during clear aligner treatment. Fausto et al. (10) observed a considerable frequency of surface wear (53%) and failure (24%), while Yaosen et al. (11) reported an average attachment loss rate of 6.7%. Lin et al. (12) reported a 1-year attachment damage rate of 14.79% for first-class and 9.70% for posterior-class attachments (overall 12.22%). Weckmann et al. (13) analyzed 125 samples and 24% were lost. The attachment loss rate observed in the present study (4.9%) was lower than those reported in previous investigations, which ranged from 6.7% to 24% (10-13). Factors that may explain the lower loss rate include the use of high-viscosity composite with increased filler content, which improves adaptation and reduces polymerization shrinkage. Strict adherence to the manufacturer's bonding protocol minimized errors and contamination. The patients were instructed to wear aligners 20-22 hours daily and trained in proper insertion and removal, reducing mechanical stress on attachments. Additionally, the incorporation of optimized attachments in our sample, which showed superior retention compared

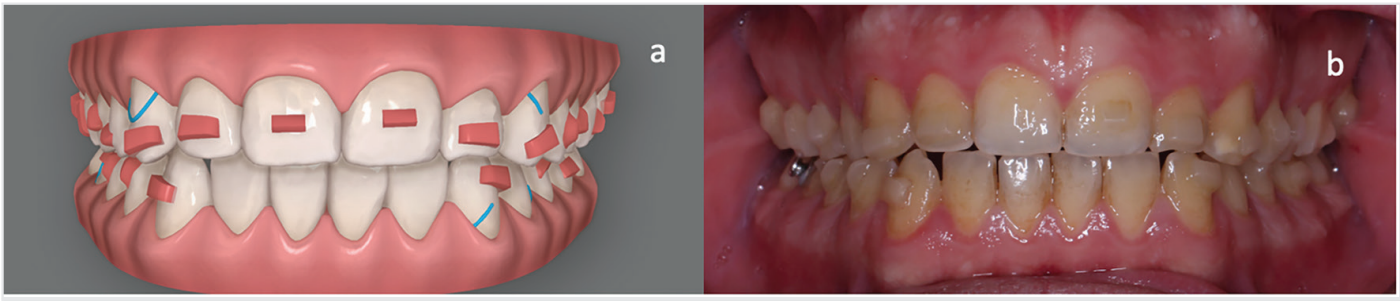

Figure 2. a) Conventional attachment planned on the maxillary right central incisor (tooth #11), b) intraoral photograph showing attachment loss on the same tooth

Table 1. Incidence of attachment loss according to patient-related factors

Factors	Outcome*		Total	p-value
	Loss	Retained		
Sex				
Female	8 (47.1)	9 (52.9)	17 (81)	1.000[c]
Male	2 (50)	2 (50)	4 (19)	
Daily aligner wear				
≤18 hour	0 (0)	1 (100)	1 (4.8)	1.000[c]
>18 hour	10 (50)	10 (50)	20 (95.2)	
Removal direction				
Buccal	1 (100)	0 (0)	1 (4.8)	0.476[c]
Lingual	9 (45)	11 (55)	20 (95.2)	
Unilateral chewing				
Right	1 (33.3)	2 (66.7)	3 (14.3)	0.754[a]
Left	2 (40)	3 (60)	5 (23.8)	
None	7 (53.8)	6 (46.2)	13 (61.9)	
Aligner removal frequency (per day)				
≤5	4 (50)	4 (50)	8 (38.1)	1.000[c]
>5	6 (46.2)	7 (53.8)	13 (61.9)	

[a]: Pearson chi-square, [c]: Fisher's exact test, *: n (%)

to conventional designs, likely contributed to the reduced attachment loss. Finally, variations in study design, patient characteristics, attachment type distribution, and follow-up protocols across studies may also explain differences in reported rates of attachment loss.

Attachment loss did not differ significantly according to dental arch (p=0.355) or side of placement (p=0.105). However, a significant association was observed between tooth type and attachment loss (p<0.001). The highest attachment loss rate was observed in molars (10.6%), followed by premolars (4.2%) and incisors/canines (0.7%). This finding contrasts with the results of Lin et al. (12), who reported that tooth type did not significantly influence attachment loss. The higher loss rate observed in molars may be explained by the greater mechanical and functional forces generated during mastication, as suggested by Yaosen et al. (11). In addition, posterior teeth may be more susceptible to moisture contamination during bonding procedures and are exposed to greater mechanical stress during aligner removal, both of which may contribute to increased attachment loss.

Table 2. Incidence of attachment loss according to treatment plan-related factors

Factors	Outcome*		Total	p-value
	Loss	Retained		
Number of attachments				
>15	9 (45)	11 (55)	19 (90.5)	1.000[c]
≤15	1 (50)	1 (50)	2 (9.5)	
Use of elastics				
Yes	6 (40)	9 (60)	15 (71.4)	0.361[c]
No	4 (66.7)	2 (33.3)	6 (28.6)	
Attachment type				
Conventional	15 (8.4)	163 (91.6)	178 (41.7)	0.009[b]
Optimized	6 (2.4)	243 (97.6)	249 (58.3)	
Size of conventional attachments				
3 mm	11 (7.6)	134 (92.4)	145 (81.5)	0.453[a]
4 mm	4 (13.8)	25 (86.2)	29 (16.3)	
5 mm	0 (0)	4 (100)	4 (2.2)	

[a]: Pearson chi-square, [b]: Yates correction, [c]: Fisher's exact test, *: n (%)

Table 3. Incidence of attachment loss according to tooth related factors

Factors	Outcome* n (%)			
	Loss, n (%)	Retained, n(%)	Total, n (%)	p-value
Arch				
Maxilla	9 (3.8)	226 (96.2)	235 (55)	0.355[b]
Mandible	12 (6.3)	180 (93.8)	192 (45)	
Side				
Right	14 (7)	187 (93)	201 (47.1)	0.105[b]
Left	7 (3.1)	219 (96.9)	226 (52.9)	
Tooth type				
Incisor/canine	1 (0.7)	152 (99.3)	153 (35.8)	0.0005[a]
Premolar	6 (4.2)	136 (95.8)	142 (33.3)	
Molar	14 (10.6)	118 (89.4)	132 (30.9)	

[a]: Pearson chi-square, [b]: Yates correction, *: n (%)

The type and properties of the composite used for attachment bonding play a crucial role in attachment retention (13). In our study, a high-viscosity composite was used which provides good adaptation to the attachment template and minimizes void formation. In line with this, Lopez et al. (14) demonstrated that dental composites with higher filler content exhibited lower polymerization shrinkage, resulting in stronger bonding to the tooth surface. This finding emphasizes that composite selection is an important factor in clinical practice, as materials with higher filler content may enhance attachment stability and reduce the risk of early attachment loss. While low-viscosity (flowable) composites may facilitate easier handling, they are more prone to surface irregularities and potential bonding failure. Thus, careful consideration of composite type, along with proper bonding technique, is essential for optimizing attachment longevity and treatment predictability.

No significant differences were observed between patients with and without attachment loss regarding gender, chewing habits, daily aligner wear time, removal frequency, or removal direction. Yaosen et al. (11) reported that frequent removal and reinsertion of aligners increased stress on attachments, and while less than five removals per day did not affect attachment loss, more frequent removal increased risk of attachment loss. In our clinic, patients were instructed to wear aligners at least 20-22 hours per day, in accordance with manufacturer recommendations, which might explain why daily wear time did not affect attachment loss incidence.

Previous studies did not evaluate the effect of elastic use, attachment type, or conventional attachment size on attachment loss (10-12). In this study, no significant differences were observed in attachment loss between patients using elastics and those not using them, nor regarding total attachment number or conventional attachment size ($p>0.05$). However, a significant difference was found regarding attachment type ($p=0.009$), with conventional attachments exhibiting higher loss than optimized attachments. Optimized attachments are individualized to tooth morphology, which may improve adaptation and reduce occlusal interference, potentially explaining the lower loss rates. Conventional attachments, having standard shapes and sizes, may adapt less effectively, leading to higher rates of attachment loss. Manual placement of conventional attachments during treatment planning may also fail to eliminate occlusal conflicts, further increasing the risk of loss. Fausto et al. (10) reported more surface wear in conventional attachments, particularly on mandibular and anterior teeth, with adhesive failure observed in 10% of samples, mostly in conventional attachments.

The results of this study underline the clinical relevance of attachment selection in clear aligner therapy. The significantly lower loss rate observed with optimized attachments suggests that careful consideration of attachment type during digital treatment planning may help minimize loss, particularly during the early stages of treatment when it occurs most frequently. These findings suggest that clinicians may consider prioritizing optimized attachment designs in certain cases, though further studies are needed.

Study Limitations

The limitations of this study include the relatively small sample size and the six-month follow-up period. Although the early phase of clear aligner therapy is clinically relevant, as attachment loss is most likely to occur during the initial stages of treatment, longer follow-up periods are necessary to evaluate long-term attachment survival. The limited sample size may reduce statistical power, particularly for subgroup analyses, and may restrict the generalizability of the findings. In addition, the absence of standardized intraoral photographic documentation and formal intra-rater reliability assessment should be taken into account evaluating the study outcomes. Overall, these limitations should be considered when interpreting the findings, particularly regarding their generalizability and long-term clinical applicability.

Conclusion

This prospective clinical study suggests that optimized attachments exhibit superior clinical survival compared with conventional attachments during the initial phase of clear aligner treatment. In addition, attachment loss was significantly associated with tooth type, with molars demonstrating the highest loss rate. These findings support the role of digital treatment planning in improving attachment performance while highlighting the influence of tooth-related biomechanical factors on attachment stability. Further large-scale, long-term prospective studies are needed to confirm these findings and to establish evidence-based guidelines for attachment selection in aligner therapy.

Ethics

Ethics Committee Approval: The study protocol and informed consent process were conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of Bezmialem Vakıf University (approval no: 2022/19, date: 18.01.2022).

Informed Consent: Written informed consent was obtained from all participants prior to enrollment.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: Ş.Ş., H.Ü., Concept: Ş.Ş., G.K., Design: Ş.Ş., G.K., Data Collection or Processing: H.Ü., Analysis or Interpretation: Ş.Ş., G.K., Literature Search: Ş.Ş., H.Ü., Writing: Ş.Ş.

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Original Article

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The Relationship Between Hounsfield Unit and Flexible URS Clinical Outcomes: A Single-center Experience

Hounsfield Ünitesi ile Esnek URS Klinik Sonuçları Arasındaki İlişki: Tek Merkezli Bir Deneyim

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ABSTRACT

Objective: This study aimed to evaluate the relationship between Hounsfield unit (HU) and clinical outcomes after flexible ureteroscopy (fURS), including stone-free rate (SFR), operative time, and postoperative complications.

Methods: A total of 300 adult patients who underwent fURS for unilateral renal stones <20 mm between January 2020 and May 2025 were retrospectively analyzed. Demographic characteristics, stone parameters, and perioperative data were recorded. The primary outcome was SFR assessed at 4-6 weeks; residual fragments <4 mm were considered clinically insignificant. Continuous variables were compared using independent-samples t-test or Mann-Whitney U test as appropriate, and categorical variables using chi-square or Fisher's exact test. Multivariable logistic regression identified predictors of SFR and postoperative complications. Receiver operating characteristic analysis was performed to evaluate the predictive value of HU for prolonged operative time, defined as durations exceeding the median operative time.

Results: Mean HU was 948±290, mean stone size was 11.8±4.9 mm, and overall SFR was 80.7%. Larger stone size significantly reduced the likelihood of achieving SFR, while stone multiplicity showed borderline significance. Age, sex, body mass index, and hydronephrosis were not significant predictors. Postoperative complications occurred in 14.8% of patients, and ureteral access sheath use significantly reduced complication risk. HU demonstrated moderate discriminatory ability for predicting prolonged operative duration.

ÖZ

Amaç: Bu çalışmada Hounsfield ünitesi (HU) ile fleksibl üreteroskopi (fURS) sonrası klinik sonuçlar arasındaki ilişkinin; taşsızlık oranı (SFR), operasyon süresi ve postoperatif komplikasyonlar açısından değerlendirilmesi amaçlandı.

Yöntemler: Ocak 2020-Mayıs 2025 tarihleri arasında tek taraflı ve <20 mm renal taş nedeniyle fURS uygulanan 300 erişkin hasta retrospektif olarak analiz edildi. Demografik özellikler, taş parametreleri ve perioperatif veriler kaydedildi. Primer sonuç ameliyat sonrası 4-6. haftada değerlendirilen SFR idi; 4 mm'den küçük artık fragmanlar klinik olarak önemsiz kabul edildi. Sürekli değişkenler uygun olduğunda bağımsız örneklem t-testi veya Mann-Whitney U testi ile, kategorik değişkenler ise ki-kare veya Fisher'in kesin testi ile karşılaştırıldı. Taşsızlık ve komplikasyonların prediktörleri çok değişkenli lojistik regresyon ile değerlendirildi. HU'nun uzamış operasyon süresini öngörme gücü alıcı işletim karakteristiği analizi ile incelendi.

Bulgular: Ortalama HU değeri 948±290, taş boyutu 11,8±4,9 mm olup genel SFR %80,7 idi. Daha büyük taş boyutu taşsızlık olasılığını anlamlı şekilde azaltırken taş çokluğu sınırda anlamlılık gösterdi. Yaş, cinsiyet, vücut kitle indeksi ve hidronefroz anlamlı prediktörler değildi. Postoperatif komplikasyon oranı %14,8 olup üreteral erişim kılıfı kullanımı komplikasyon riskini anlamlı şekilde azalttı. HU'nun uzamış operasyon süresini öngörme gücü orta düzeyde bulundu.

Sonuç: HU, fURS sonrası operasyon zorluğunu öngörmede klinik açıdan anlamlı bir parametredir. Taş boyutu ve anatomik

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ABSTRACT

Conclusion: HU is a clinically meaningful indicator of procedural complexity following fURS. Incorporating HU together with stone size and anatomical factors may improve preoperative planning, surgical decision-making, and patient counseling.

Keywords: Hounsfield unit, flexible ureteroscopy, stone-free rate, operative time, renal calculi

ÖZ

faktörlerle birlikte değerlendirilmesi, preoperatif planlama ve hasta bilgilendirmesini iyileştirebilir.

Anahtar Kelimeler: Hounsfield ünitesi, fleksibl üreteroskopi, taşsızlık oranı, operasyon süresi, renal taş

Introduction

Hounsfield unit (HU), a quantitative parameter derived from non-contrast computed tomography (CT), reflects tissue density and provides valuable information regarding stone hardness and crystalline composition (1,2). The well-established association between HU and stone structure has positioned this metric as an essential component of preoperative decision-making in contemporary endourological practice (3-5).

Flexible ureteroscopy (fURS) has become a widely adopted treatment modality for small and moderate renal stones, offering high stone-free rates (SFR) with low morbidity. However, procedural difficulty and treatment efficacy vary considerably across patients. Higher HU values and certain anatomical factors—particularly lower pole configuration—have consistently been associated with increased procedural complexity, prolonged operative duration, and reduced SFRs (6-9). These observations suggest that stone density may play a more critical role in determining surgical difficulty and postoperative outcomes than traditionally assumed.

Given the increasing emphasis on individualized surgical planning and outcome optimization, understanding the predictive value of HU in fURS is of significant clinical importance. Therefore, this study aimed to investigate the relationship between HU and key clinical outcomes—including stone-free status, operative duration, and postoperative morbidity—in a single-center retrospective cohort of patients undergoing fURS.

Methods

A retrospective review was conducted on 300 consecutive adult patients who underwent fURS at our institution between January 2020 and May 2025. Patients younger than 18 years, those with bilateral renal stones, stones larger than 20 mm, congenital or acquired renal anatomical anomalies (such as horseshoe kidney, pelvic kidney, or duplicated collecting system), concurrent surgical procedures during the same session, incomplete radiological or clinical data, or postoperative follow-up shorter than 4 weeks were excluded.

Collected variables included demographic characteristics [age, sex, and body mass index (BMI)]; stone characteristics (stone size, mean HU, and anatomical location categorized as lower pole, mid pole, renal pelvis, or upper pole); stone multiplicity; presence of hydronephrosis; and pre-stenting status.

All procedures were performed using a 7.5F fURS (HugeMed) and the same holmium: YAG laser platform, with standardized laser settings of 1.2 J energy and 15 Hz frequency. A 273-µm disposable laser fiber was used in all patients to ensure uniformity of laser fragmentation technique. Dusting or fragmentation strategies were selected according to intraoperative visibility and stone response. The use of a ureteral access sheath (UAS) was left to the discretion of the operating surgeon.

Stone density was measured using non-contrast CT performed with a 64-slice scanner. HU measurements were obtained on axial images by placing a 3-5 mm circular region of interest (ROI) over the largest cross-sectional area of the stone while avoiding partial-volume effects. The mean HU value was recorded for analysis.

The primary outcome was the SFR at 4-6 weeks postoperatively. Stone-free status was assessed primarily using non-contrast CT, which represents the standard follow-up imaging modality at our institution. In selected cases, ultrasonography or kidney-ureter-bladder (KUB) radiography was used according to routine clinical follow-up protocols when CT was not considered clinically necessary. Residual fragments smaller than 4 mm were considered clinically insignificant. Secondary outcomes included postoperative complications classified according to the Clavien-Dindo system.

Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Aksaray University Health Sciences Scientific Research Ethics Committee (decision no: 2025/200, protocol no: SAGETİK 2025-129, date: 09.10.2025). Because the study was retrospective and based on anonymized data, the requirement for written informed consent was waived by the committee.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0. Data normality was assessed with the Shapiro-Wilk test. Continuous variables were compared using the independent-samples t-test or Mann-Whitney U test, and categorical variables using the chi-square or Fisher's exact test as appropriate. Multivariable logistic regression analysis was used to identify predictors of stone-free status and postoperative complications. Receiver operating characteristic (ROC) analysis evaluated the predictive value of HU for prolonged operative time. A p-value <0.05 was considered statistically significant.

Results

A total of 300 patients who underwent fURS were included in the analysis. The mean age was 46.8±13.5 years, and 57% of the cohort were male. The mean BMI was 27.4±3.9 kg/m², the mean stone size was 11.8±4.9 mm, and the mean stone density was 948±290 HU (Figure 1). Lower pole stones accounted for 50% of all cases, while 21% of patients had multiple stones, and 18% underwent pre-stenting prior to the procedure. The mean operative time was 71.9±22 minutes, and the overall SFR at 4-6 weeks was 80.7%. Baseline demographic and stone characteristics are presented (Table 1).

Multivariable logistic regression analysis demonstrated that larger stones were associated with reduced SFR [odds ratio (OR)=0.90; 95% confidence interval: 0.8-1.0; p=0.01]. Stone multiplicity showed a borderline association with lower SFR (OR=0.57; p=0.07), while hydronephrosis, age, sex, and BMI were not significant predictors. In the location analysis, stones in the mid pole (OR=3.58; p<0.001), renal pelvis (OR=3.22; p=0.01), and upper pole (OR=2.70; p=0.02) demonstrated higher odds of achieving SFR compared with lower pole stones, which were used as the reference category in the model. Full regression results are summarized (Table 2).

None of the other evaluated variables—including, stone size, multiplicity, hydronephrosis, sex, BMI, age, or operative time—were significantly associated with postoperative complications, and stone location likewise did not demonstrate a significant effect (Table 3).

To further explore the influence of stone density on procedural difficulty, a ROC analysis was performed to evaluate the ability of HU to predict prolonged operative time, defined as a duration above the median. The relationship between HU and operative time is illustrated (Figure 2), and HU demonstrated moderate discriminative ability for identifying longer procedures (Figure 3).

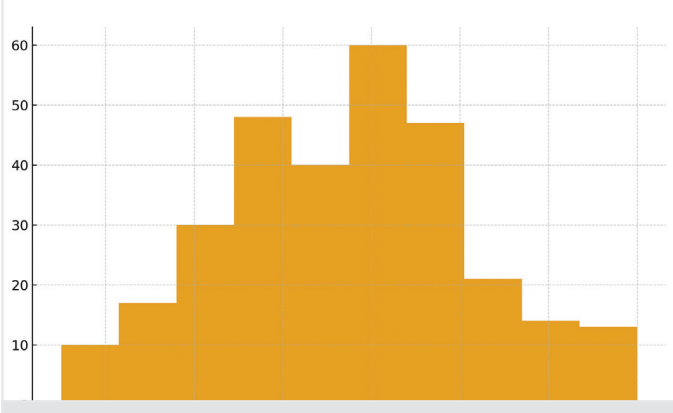

Figure 1. Distribution of stone density (HU)

Histogram showing the distribution of HU values measured on non-contrast CT in the study population

HU: Hounsfield unit, CT: Computed tomography

Table 1. Baseline demographic, stone, and operative characteristics

Variable	Value
Age (years, mean ± SD)	46.8±13.5
Sex (male/female)	57%/43%
BMI (kg/m²)	27.4±3.9
Stone size (mm)	11.8±4.9
Stone density (HU)	948±290
Lower pole stones (%)	50%
Multiple stones (%)	21%
Pre-stented (%)	18%
Operative time (min, mean ± SD)	71.9±22
Stone-free rate (%)	80.7%

Note: Values are presented as mean ± standard deviation or percentage
SD: Standard deviation, BMI: Body mass index, HU: Hounsfield unit

Table 2. Multivariable logistic regression analysis predicting stone-free status

Predictor	OR	95% CI	p-value
Intercept	28.74	2.1-392.2	0.01
Mid pole vs. lower pole (reference)	3.58	1.6-8.0	0.001
Renal pelvis vs. lower pole	3.22	1.4-7.3	0.01
Upper pole vs. lower pole	2.70	1.2-6.2	0.02
Male sex	0.74	0.4-1.3	0.33
Stone size (mm)	0.90	0.8-1.0	0.01
Multiple stones	0.57	0.3-1.0	0.07
Pre-stented	1.32	0.7-2.4	0.37
Hydronephrosis	0.82	0.4-1.5	0.51
BMI	1.04	1.0-1.1	0.26
Age	0.99	1.0-1.0	0.45

Note: Lower pole location used as reference category
OR: Odds ratio, CI: Confidence interval, BMI: Body mass index

Table 3. Multivariable logistic regression analysis predicting postoperative complications (Clavien >0)

Predictor	OR	95% CI	p-value
Intercept	0.03	0.0-2.2	0.11
Mid pole vs lower pole (reference)	0.85	0.3-2.8	0.79
Renal pelvis vs lower pole	1.12	0.3-3.8	0.86
Upper pole vs lower pole	0.86	0.2-3.0	0.82
Male sex	0.98	0.4-2.3	0.96
Stone size (mm)	1.07	1.0-1.2	0.22
Multiple stones	0.65	0.3-1.5	0.31
Pre-stented	0.82	0.3-1.9	0.64
Hydronephrosis	0.95	0.4-2.2	0.91
BMI	0.95	0.9-1.0	0.31
Age	1.01	1.0-1.0	0.46
Operative time	1.01	1.0-1.0	0.21
Access sheath used	0.21	0.1-0.5	<0.001

OR: Odds ratio, CI: Confidence interval, BMI: Body mass index

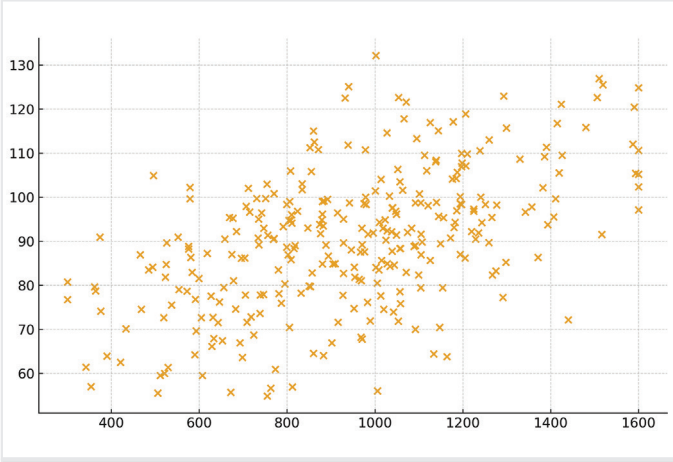

Figure 2. Relationship between HU and operative time

Scatter plot illustrating the association between stone density (HU) and operative duration during flexible ureteroscopy

HU: Hounsfield unit

Discussion

Our findings demonstrated that stone density, quantified by HU on non-contrast CT, is relevant to procedural complexity following fURS. The substantial variation in HU values in our cohort reflects heterogeneous stone composition and reinforces its relevance as a preoperative indicator of fragmentation difficulty and procedural complexity (1-5). In the present study, HU demonstrated moderate discriminatory ability for prolonged operative duration, supporting the role of stone density in preoperative assessment of procedural complexity (6-9).

The overall SFR (80%) observed in our study aligns with previously published rates ranging from 75% to 85% (1-3,8,9). Stone size also negatively influenced stone-free outcomes, while stone multiplicity demonstrated borderline statistical significance. These findings are consistent with previously developed scoring systems such as the Resorlu-Unsal score and the R.I.R.S. scoring system, both of which incorporate stone burden into predictive models of surgical success (10-13).

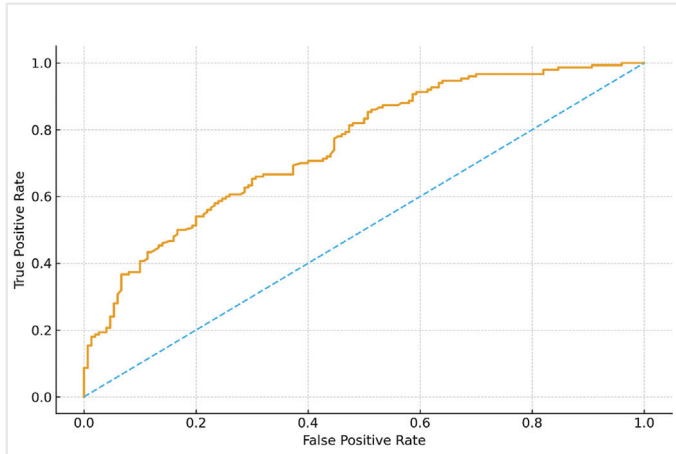

Figure 3. ROC curve for HU predicting prolonged operative time (AUC=0.75)

ROC curve demonstrating the discriminative ability of HU in predicting operative duration exceeding the median operative time

ROC: Receiver operating characteristic, HU: Hounsfield unit, AUC: Area under the curve

Previous literature has highlighted additional CT-based predictors of surgical complexity. Traxer and Thomas (14) emphasized the importance of preoperative ureteral evaluation, while systematic reviews examining UAS use have demonstrated its potential benefits in facilitating ureteroscopy and improving intraoperative conditions (15). Furthermore, HU-based threshold values proposed in earlier studies and reports linking higher stone density with procedural difficulty support the clinical relevance of CT-derived attenuation measures in endourological planning (16-20).

Beyond density alone, CT-derived attenuation parameters and skin-to-stone distance have also been associated with lithotripsy success and procedural difficulty. These findings collectively support the view that HU is not only a marker of stone composition but also an indicator of procedural complexity (21).

Postoperative complication rates in our cohort were low and limited to minor-to-moderate events, consistent with previous fURS series. Notably, UAS use significantly reduced complication rates. This observation likely reflects improved irrigation flow, reduced intrarenal pressure, and enhanced intraoperative visibility, mechanisms previously demonstrated in experimental and clinical studies (22,23). The absence of major complications further supports the

safety profile of fURS even in patients with higher-density stones.

Another important finding of this study was the moderate predictive value of HU for prolonged operative duration. Denser stones often require longer laser fragmentation time and increased intraoperative manipulation. Emerging machine-learning-based predictive models have been explored in urinary stone disease, supporting the broader potential of data-driven approaches in individualized endourological decision-making (24,25).

Taken together, these findings reinforce the clinical value of HU as a preoperative indicator of procedural complexity that may enhance surgical planning, optimize intraoperative strategy, and improve patient counseling.

Study Limitations

This study has several limitations. First, its retrospective single-center design may introduce selection bias and may limit the generalizability of the findings. Second, patients with congenital or acquired renal anatomical anomalies were excluded, which may restrict applicability to more complex anatomical scenarios. Third, long-term postoperative outcomes—such as ureteral stricture formation or delayed complications—were not evaluated. Additionally, although HU measurements were standardized using consistent ROI placement, inter-observer variability may still occur in routine clinical practice.

Another limitation is the use of different imaging modalities for postoperative stone-free assessment. Although non-contrast CT was the primary follow-up method at our institution, ultrasonography or KUB radiography was used in selected cases according to routine clinical practice. This heterogeneity may have influenced the accuracy of SFR evaluation.

Prospective multicenter studies with longer follow-up are needed to further validate the predictive role of HU in fURS.

Conclusion

HU is a clinically relevant indicator of procedural complexity following fURS. HU demonstrated moderate discriminatory ability for prolonged operative duration, indicating increased procedural complexity with denser stones. Stone size remains an important determinant of treatment success, while the use of a UAS appears to reduce postoperative complications. Incorporating HU into preoperative assessment may support surgical planning, improve patient counseling, and optimize case selection. Further prospective multicenter studies integrating HU with anatomical parameters and advanced predictive models are needed to refine clinical decision-making in endourology.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Aksaray University Health Sciences Scientific Research Ethics Committee (decision no: 2025/200, protocol no: SAGETİK 2025-129, date: 09.10.2025).

Informed Consent: As the study was retrospective and based on anonymized data, the requirement for written informed consent was waived by the committee.

Footnotes

Authorship Contributions

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

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

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

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Case Report

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Bezmialem Science 2026;14(3):307-311

Colloid Cyst of the Posterior Fossa: A Case Report and Review of the Literature

Posterior Fossa Kolloid Kisti: Olgu Sunumu ve Literatür Taraması

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ABSTRACT

Colloid (neuroepithelial) cysts are slow-growing, benign, potentially fatal lesions that account for less than 2% of all intracranial tumors. They are most commonly located in the third ventricle, however may be seen along the entire neural axis. A 39-year-old woman presented with a one-year history of increasingly frequent headaches. She had no neurological signs. On magnetic resonance imaging, a cystic mass was observed in the left cerebellum (24×21×20 mm) compressing the fourth ventricle and brainstem. The cystic mass was totally excised, and histopathology confirmed a colloid cyst. The patient was discharged with no neurological deficit. Colloid cysts are very rare in the posterior fossa. The most common symptom is headache. Its origin is not known exactly, but it is thought to develop as a result of abnormal folding of the primitive neuroepithelium. Total excision of colloid cysts is curative.

Keywords: Colloid cyst, neuroepithelial cyst, posterior fossa

ÖZ

Kolloid (nöroepitel) kistler, tüm intrakranial tümörlerin %2'sinden daha azını oluşturan, yavaş büyüyen, iyi huylu, potansiyel olarak ölümcül lezyonlardır. En sık üçüncü ventrikülde yerleşirler, ancak tüm nöral aks boyunca görülebilirler. Otuz dokuz yaşında bir kadın, bir yıldır giderek sıklaşan baş ağrısı öyküsü ile başvurdu. Nörolojik belirtisi yoktu. Manyetik rezonans görüntülemede, sol serebellumda (24×21×20 mm) dördüncü ventrikülü ve beyin sapını sıkıştıran kistik bir kitle görüldü. Kistik kitle tamamen çıkarıldı ve histopatoloji kolloid kisti doğruladı. Hasta nörolojik defisit olmadan taburcu edildi. Kolloid kistler posterior fossada çok nadir görülür. En sık görülen semptom baş ağrısıdır. Kökeni tam olarak bilinmemektedir, ancak ilkel nöroepitelyumun anormal katlanması sonucu geliştiği düşünülmektedir. Kolloid kistlerin total eksizyonu küratiftir.

Anahtar Kelimeler: Kolloid kist, nöroepitelyal kist, posterior fossa

Introduction

Colloid (neuroepithelial) cysts are slow-growing, benign lesions that account for less than 2% of all intracranial tumors, yet they can be potentially fatal (1,2). They are typically located within the third ventricle, near the foramen of Monro. However, on rare occasions, they can be found along the entire neural axis (3-7). A posterior fossa location is exceptionally rare, and this atypical localization presents both diagnostic and therapeutic challenges. While third ventricle cysts typically present with obstructive hydrocephalus and related symptoms (headache, changes in consciousness, seizures, nausea, dizziness, and even sudden death) (2,8,9), cysts in the posterior fossa are more likely to manifest with clinical signs of brainstem and cerebellar compression. Therefore, when a cystic lesion is detected in the posterior fossa, the differential diagnosis is broad, and advanced neuroimaging methods play a critical role in reaching an accurate diagnosis. Specifically,

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multi-parametric magnetic resonance imaging (MRI) is the cornerstone for characterizing the lesion, establishing the surgical indication, and determining the treatment strategy. In this case report, we present a rare case of a colloid cyst located in the posterior fossa, aiming to discuss the diagnostic nuances, treatment management, and particularly the importance of specific imaging modalities in the decision-making process, supported by a literature review.

Case Report

A 39-year-old woman presented with a one-year history of progressively worsening headaches. Her neurological examination revealed no focal neurological deficits, and a funduscopic examination confirmed the absence of papilledema. MRI of the brain revealed a 24×21×20 mm cystic mass in the left cerebellum, compressing the fourth ventricle and brainstem. The lesion appeared hypointense on T1-weighted images and hyperintense on T2-weighted images. The signal characteristics of colloid cysts can vary depending on the cyst's contents, such as protein, mucin, or blood products, and their viscosity, which can lead to appearances different from the typical T1 hyperintensity. The lesion was hyperintense on fluid-attenuated inversion recovery (FLAIR) sequences, and diffusion-weighted imaging (DWI) with the corresponding apparent diffusion coefficient (ADC) map showed no diffusion restriction. No contrast enhancement was observed (Figure 1). The patient underwent a suboccipital craniotomy. The intraoperative appearance of the lesion was consistent with the preoperative MRI findings. The thin-walled cystic mass was excised using microsurgical techniques via a transvermian approach. This approach was chosen due to the cyst's superior extension and its relationship to the midline, providing a direct surgical corridor while

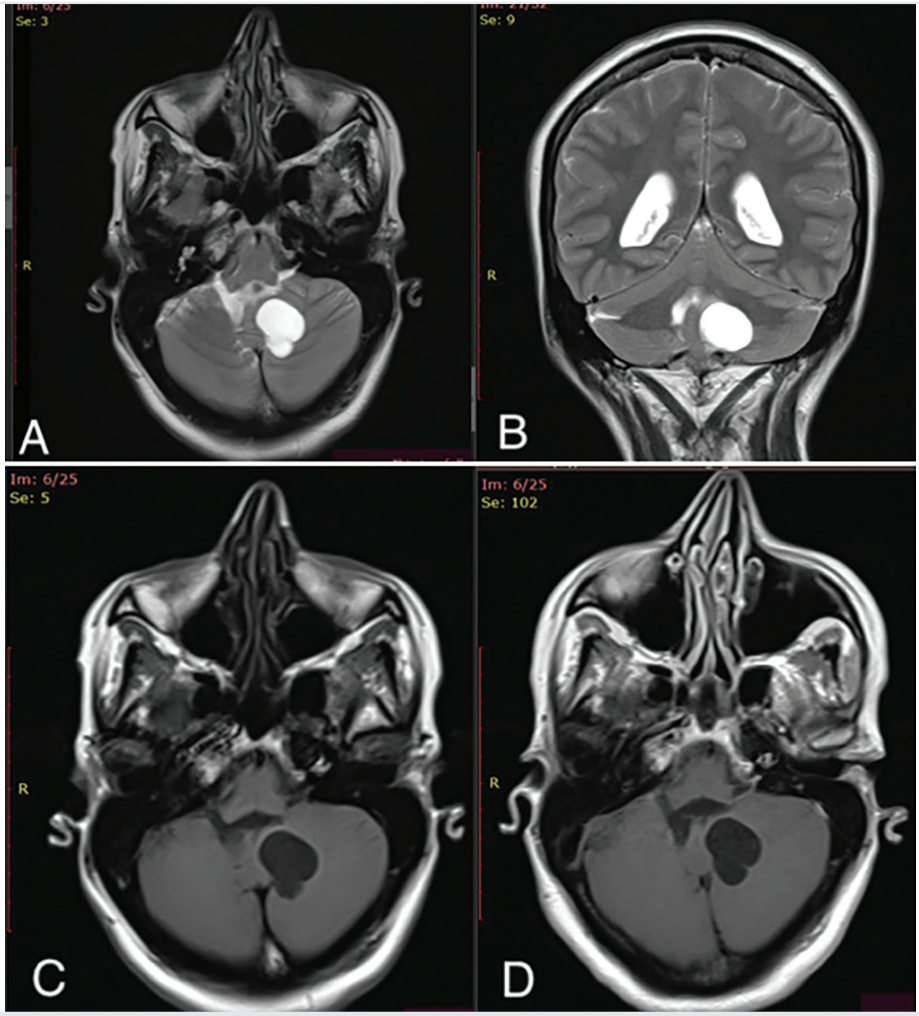

Figure 1. MRI revealing a well-defined cystic lesion in the left cerebellum. (A) Axial T2-weighted image and (B) coronal T2-weighted image demonstrate a hyperintense cystic measuring 24×21×20 mm. (C) Axial T1-weighted image shows the lesion as hypointense, and (D) axial contrast-enhanced T1-weighted image shows no enhancement of the cyst. The lesion causes compression of the fourth ventricle and brainstem

MRI: Magnetic resonance imaging

respecting the surrounding venous anatomy. The telovelar approach is also a reasonable alternative for accessing the fourth ventricle, particularly for more inferiorly located lesions, as it spares the vermis. The patient recovered well postoperatively and was discharged without any neurological deficits. Histopathological examination confirmed the lesion was a colloid cyst. Microscopic examination revealed benign epithelial fragments within the cerebellar tissue. The cyst lining consisted of an epithelial layer that was composed of partly a single layer of flat or cuboidal cells and partly low columnar cells. Immunohistochemical staining showed that the epithelial component was positive for epithelial membrane antigen (EMA) and pancytokeratin, while it was negative for glial fibrillary acidic protein (GFAP) and S-100. The surrounding cerebellar parenchyma was positive for GFAP and S-100 (Figure 2). Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

Discussion

Colloid (neuroepithelial) cysts are slow-growing, benign, yet potentially fatal lesions, accounting for less than 2% of all intracranial tumors (1,2). Although they are most commonly located in the third ventricle, they can be seen along the entire neural axis (3-7). They are exceedingly rare in the posterior fossa (5). The most common symptom is headache. Other reported symptoms include gait disturbance, loss of consciousness, nausea

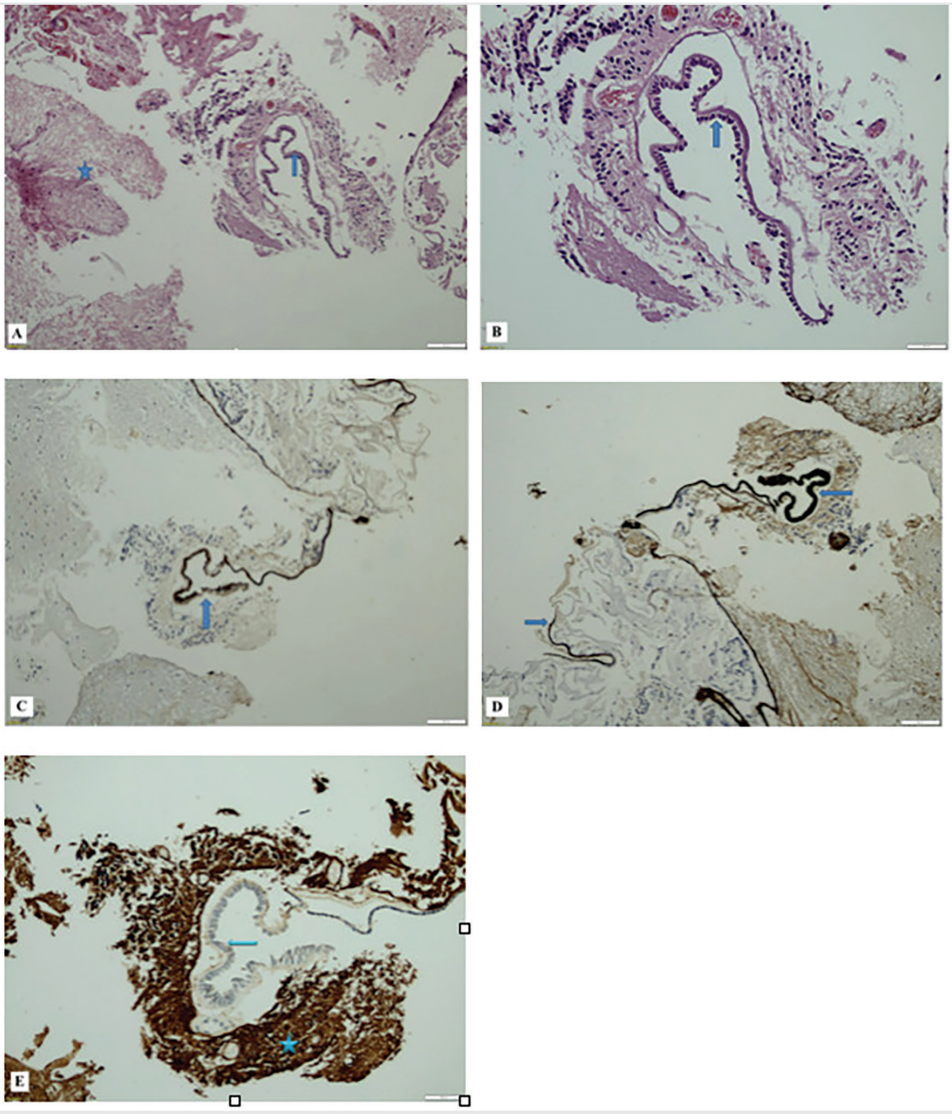

Figure 2. Histopathological images of the resected colloid cyst and surrounding cerebellar tissue. (A and B) H&E-stained sections showing a cyst wall fragment with a single layer of epithelial cells (arrow) adjacent to cerebellar parenchyma (star). (C and D) Immunohistochemical staining for epithelial markers shows strong positivity for EMA and pancytokeratin in the cyst's epithelial lining (arrows). (E) GFAP staining is positive in the surrounding cerebellar tissue (star) but negative in the cyst epithelium (arrow)

EMA: Epithelial membrane antigen, GFAP: Glial fibrillary acidic protein, H&E: Hematoxylin and eosin

and vomiting, visual disturbances, urinary incontinence, dizziness, seizures, and diplopia. Despite being benign, they can cause acute hydrocephalus and sudden death (10). The most common clinical finding is papilledema (11).

The exact origin of colloid cysts is unknown, but they are thought to develop from an abnormal folding of the primitive neuroepithelium. The cyst contents typically include mucin, hemosiderin, cholesterol, and various ions (12). Histologically, colloid cysts (also known as neuroepithelial cysts) consist of an outer fibrous capsule and an inner single layer of squamous, cuboidal, or low columnar epithelium (6). They typically show positive staining with periodic acid-Schiff, EMA, and cytokeratin, and they are negative for GFAP and S-100 (3).

The Role of Imaging Modalities in Diagnosis and Treatment Decisions

In addition to clinical findings, advanced neuroradiological examinations played a critical role in making the surgical treatment decision and in preoperative planning. The multi-parametric MRI sequences used in our case were fundamental in understanding the nature of the lesion and narrowing the differential diagnosis. The lesion's hypointense appearance on T1-weighted series and hyperintense appearance on T2-weighted series, while different from the typical T1 hyperintense signal of classic third ventricle colloid cysts, confirms that signal characteristics can be variable depending on the protein and mucin concentration of the cyst contents. The hyperintensity of the lesion on the fluid-attenuated FLAIR sequence confirmed that the cyst content was different from cerebrospinal fluid (CSF), ruling out lesions with the same signal intensity as CSF, such as an arachnoid cyst. The absence of diffusion restriction on DWI and the ADC map, one of the most critical sequences, allowed us to exclude an epidermoid cyst, which is one of the most important differential diagnoses in this region and typically shows marked diffusion restriction. Finally, the lack of any contrast enhancement in the lesion on post-contrast series was interpreted against cystic neoplasms such as hemangioblastoma, pilocytic astrocytoma, or ependymoma, which typically show enhancement in a mural nodule or solid components. This multi-parametric MRI approach revealed the benign, non-neoplastic cystic nature of the lesion, which, combined with its compression of the brainstem and fourth ventricle, finalized the indication for surgical excision.

Differential Diagnosis and Surgical Management

The differential diagnosis for a cystic lesion in the posterior fossa is broad. It includes epidermoid and dermoid cysts, which typically demonstrate diffusion restriction; arachnoid cysts, which follow CSF signal on all sequences; and rare neurenteric cysts, which are often located ventral to the brainstem. Furthermore, cystic tumors such as hemangioblastoma, pilocytic astrocytoma, and ependymoma should also be considered, though these were ruled out in our case by the absence of an enhancing mural nodule or solid component (9).

To our knowledge, five cases of colloid cysts in the posterior fossa were previously reported in the literature (4-6,13). The mean age of all six cases (including the present case) was 39.6 years. All cases presented with headache. All cases showed compression of the brainstem and fourth ventricle, and all were treated surgically. In all patients, including our own, the preoperative neurological symptoms improved after treatment. The details of the previously reported posterior fossa colloid cyst cases are summarized in Table 1.

There is no consensus on the management of colloid cysts. Symptomatic colloid cysts are best treated with surgical excision. The management of incidental, asymptomatic, or non-hydrocephalic colloid cysts is controversial. It should be kept in mind that colloid cysts may cause acute hydrocephalus and therefore require urgent shunting. Complete surgical excision of colloid cysts is curative, and recurrence is rare (14).

Conclusion

Although rare, colloid cysts of the posterior fossa should be considered in the differential diagnosis of intracranial lesions in this region. Given that they can compress the brainstem and fourth ventricle and become symptomatic, surgical treatment is recommended upon diagnosis. multi-parametric MRI is an indispensable tool for achieving an accurate diagnosis and determining the surgical strategy.

Table 1. Summary of reported posterior fossa colloid cyst cases in the literature

Reference, year	Age/gender	Cases	Symptom	Fourth ventricle/ brainstem compression
Romero et al. (4), 1987	14/M	1	H/A, nausea	+
Tada et al. (5), 1993	44/F	1	H/A, nausea, gait disturbance	+
Müller et al. (6), 1999	45/F	1	H/A, nausea, gait disturbance	+
Andrews et al. (13), 1984	31/M 65/M	2	Hearing loss, facial paresthesia Vertigo, diplopia	+ +
Present study	39/F	1	H/A	+

M: Male, F: Female, H/A: Headache

Ethics

Informed Consent: Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

Footnotes

Authorship Contributions

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

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

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Review

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A Comprehensive Review of Addiction: Historical Development, Neurobiological Foundations, Diagnostic Criteria, and Organizations Responsible for Combating Addiction

Bağımlılığa Kapsamlı Bir Bakış: Tarihsel Gelişim, Nörobiyolojik Temeller, Tanı Kriterleri ve Bağımlılıkla Mücadeleden Sorumlu Kuruluşlar

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ABSTRACT

Addiction is a complex and multifaceted condition that significantly affects individuals' physical, psychological, and social well-being. Beyond substance dependence, addiction encompasses behavioral disorders such as gambling, excessive technology use, and compulsive shopping. Historically, substance use has been deeply embedded in societal and cultural practices, evolving from medicinal and ritualistic applications to modern regulatory frameworks. Advances in neuroscience have elucidated the pivotal role of neurotransmitters and brain structures, particularly the reward system, in the development and persistence of addiction. While chemical addictions—such as those involving alcohol, nicotine, and illicit drugs—profoundly alter physiological processes, behavioral addictions impair impulse control and reward processing, resulting in compulsive behaviors. The diagnosis of addiction adheres to standardized frameworks, including the Diagnostic and Statistical Manual of Mental Disorders, fifth edition and the International Classification of Diseases, tenth edition, which assess severity based on behavioral patterns and physiological responses. Treatment approaches encompass pharmacological interventions and psychological therapies, with an increasing emphasis on holistic and multidisciplinary strategies. National and international organizations, such as

ÖZ

Bağımlılık, bireylerin fiziksel, psikolojik ve sosyal iyi oluşunu önemli ölçüde etkileyen karmaşık ve çok yönlü bir durumdur. Madde bağımlılığının ötesinde, bağımlılık; kumar, aşırı teknoloji kullanımı ve kompulsif alışveriş gibi davranışsal bozuklukları da içermektedir. Tarihsel olarak madde kullanımı, toplumsal ve kültürel uygulamalara derinlemesine yerleşmiş olup, tıbbi ve ritüel amaçlardan modern düzenleyici çerçevelere doğru evrim geçirmiştir. Nörobilim alanındaki ilerlemeler, nörotransmitterlerin ve özellikle ödül sisteminin bağımlılığın gelişimi ve devamlılığındaki kritik rolünü açıklığa kavuşturmuştur. Alkol, nikotin ve yasa dışı maddeler gibi kimyasal bağımlılıklar fizyolojik süreçleri derinden değiştirirken, davranışsal bağımlılıklar dürtü kontrolünü ve ödül işleyişini bozarak kompulsif davranışlara neden olmaktadır. Bağımlılığın tanısı, Ruhsal Bozuklukların Tanısal ve İstatistiksel El Kitabı, beşinci baskı ve Uluslararası Hastalık Sınıflandırması, Onuncu baskı gibi standartlaştırılmış çerçeveler doğrultusunda belirlenmekte olup, bu değerlendirmeler davranışsal örüntüler ve fizyolojik tepkiler temelinde yapılmaktadır. Tedavi yaklaşımları, farmakolojik müdahaleler ve psikolojik terapileri içermekte olup, giderek daha fazla bütüncül ve multidisipliner stratejilere odaklanılmaktadır. Dünya Sağlık Örgütü, Birleşmiş Milletler Uyuşturucu ve Suç Ofisi ve ***Yeşilay*** Cemiyeti gibi

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ABSTRACT

the World Health Organization, the United Nations Office on Drugs and Crime, and ***Yeşilay***, play a crucial role in addiction prevention, rehabilitation, and policy development. A comprehensive understanding of addiction necessitates an integrated approach that combines biological, psychological, and social perspectives. This review aims to provide an in-depth analysis of addiction and its implications for public health, guiding further research and policy advancements in the field. Future research should focus on innovative therapies and personalized treatment plans to enhance recovery outcomes.

Keywords: Behavioral addictions, diagnosis, neurobiology of addiction, substance-related disorders, preventive health services

ÖZ

ulusal ve uluslararası kuruluşlar, bağımlılığın önlenmesi, rehabilitasyonu ve politika geliştirme süreçlerinde kritik bir rol oynamaktadır. Bağımlılığın kapsamlı bir şekilde anlaşılması, biyolojik, psikolojik ve sosyal perspektiflerin birleştirilmesini gerektirmektedir. Bu derleme, bağımlılığın halk sağlığı üzerindeki etkilerini derinlemesine analiz etmeyi, alandaki araştırmaları ve politika geliştirme süreçlerini yönlendirmeyi amaçlamaktadır. Gelecekteki araştırmalar, yenilikçi terapilere ve kişiye özel tedavi planlarına odaklanarak iyileşme süreçlerini daha etkili hale getirmeye yönelmelidir.

Anahtar Kelimeler: Davranışsal bağımlılıklar, tanı, bağımlılığın nörobiyolojisi, madde ile ilişkili bozukluklar, koruyucu sağlık hizmetleri

Introduction

Addiction is a multifaceted disorder that profoundly impacts an individual's physical and psychological well-being, social interactions, and overall quality of life (1). It is defined as the compulsive engagement in substance use or behaviors despite detrimental consequences. This conceptualization underscores that addiction extends beyond substance dependence to encompass behavioral addictions, such as those related to technology, gambling, and compulsive shopping (2).

Key characteristics of addiction include the development of tolerance, withdrawal symptoms, impaired control, persistent use despite adverse effects, and altered life priorities (3). Tolerance develops when an individual requires escalating amounts of a substance or behavior to achieve the desired effect. Withdrawal symptoms, manifesting as physical and psychological distress when access to the addictive substance or behavior is restricted, contribute significantly to the perpetuation of the addiction cycle (4).

Beyond being an individual affliction, addiction represents a substantial societal concern. It disrupts family structures, undermines professional productivity, burdens healthcare systems, and imposes economic constraints. For example, substance dependence leads to escalating healthcare expenditures and diminished workforce efficiency, whereas technology addiction negatively influences interpersonal relationships and productivity levels. Moreover, addiction-related stigma presents a considerable obstacle to seeking and receiving appropriate treatment (5).

The etiology of addiction is rooted in a complex interplay of biological, psychological, and social determinants, necessitating a holistic approach to treatment (6). Biologically, genetic predisposition, dysregulated neurotransmitter activity, and neurostructural modifications contribute to addiction susceptibility. Psychologically, factors such as trauma, chronic stress, depression, and low self-esteem play a pivotal role. On a social level, inadequate familial support, social isolation, and economic hardship are significant risk factors that facilitate addiction development (7).

This review aims to provide a detailed analysis of addiction by exploring its historical evolution, different types, neurobiological underpinnings, and the criteria used for its diagnosis and evaluation. Additionally, the study examines the role of national and international organizations in monitoring and addressing addiction-related challenges. By synthesizing existing research, this review seeks to contribute to a deeper understanding of addiction as a medical, psychological, and social phenomenon, helping to inform future studies in this field.

This review was conducted as a structured narrative review. Literature was searched in PubMed, Scopus, Web of Science, Google Scholar, and the Cochrane Library. Literature searches were conducted using combinations of relevant keywords and Medical Subject Headings (MeSH), including terms related to addiction, substance use disorders, behavioral addictions, neurobiology, diagnosis, prevention, treatment, and rehabilitation. Peer-reviewed articles published in English between 2010 and 2025 were primarily considered. Seminal publications published before 2010 were included when historically or conceptually important. Studies focusing on addiction epidemiology, neurobiology, diagnostic criteria, treatment approaches, and national or international addiction organizations were included. Conference abstracts, editorials without scientific content, duplicate publications, and studies unrelated to addiction were excluded. Retrieved publications were screened according to relevance to the objectives of the review, and the selected literature was synthesized narratively.

History of Substance Use

Substance use has been a persistent aspect of human civilization, dating back to ancient times when natural substances were utilized for medicinal, ritualistic, and recreational purposes. Over the centuries, societies have developed varying perceptions and regulations regarding substance use, influenced by cultural, political, and economic factors.

Ancient and Early Uses

In antiquity, substances such as opium, cannabis, and alcoholic beverages were widely used across different civilizations for both therapeutic and religious purposes. The Sumerians, around 3000 BCE, referred to opium as the "plant of joy", employing it in religious ceremonies and medicinal practices. Similarly, alcohol was integral to social and spiritual rituals in Ancient Greece and Rome, where wine was considered sacred and widely consumed during festivals (3,8).

The Middle Ages and Substance Use

During the Middle Ages, the use of psychoactive substances remained largely medicinal and ritualistic. However, with the expansion of trade routes, opium found its way from Asia to Europe, increasing its accessibility and usage. In the Islamic world, alcohol consumption was restricted due to religious prohibitions, whereas opium continued to be used for medicinal purposes, as documented by scholars such as Avicenna (3,9).

Substance Use in the Ottoman Empire

The Ottoman Empire maintained a controlled but occasionally widespread practice of substance use. Opium cultivation and trade were integral to the economy, with Anatolia serving as a significant producer. Tobacco was introduced to the empire in the 16th century and quickly gained popularity, despite being subject to strict prohibitions during the reign of Sultan Murad IV. Although alcohol consumption remained largely underground due to Islamic laws, it was notably prevalent among non-Muslim communities (10,11).

The Republican Era and Substance Use in Türkiye

In the 20th century, Türkiye began implementing stricter regulations regarding substance use (12). By the 1930s, Türkiye aligned with international drug control policies, instituting stringent regulations on opium production and trade. The 1970s and 1980s witnessed intensified global drug trafficking concerns, prompting the Turkish government to enhance its measures against substance abuse. In contemporary Türkiye, addiction has emerged as a pressing issue, particularly among younger demographics, necessitating the establishment of treatment and prevention programs such as Alcohol and Substance Addiction Treatment Center (AMATEM) (13).

The historical evolution of substance use reflects its deep entrenchment in socio-cultural and economic structures. Türkiye's regulatory efforts highlight the ongoing need for a comprehensive, multidisciplinary approach to combating addiction at national and global levels (12).

Types of Addiction

Addiction is broadly classified into two main categories: chemical (substance addiction) and behavioral (process) addiction. Each type presents distinct mechanisms, risk factors, and consequences, necessitating tailored intervention strategies (14).

Chemical Addictions (Substance Use Disorders)

Chemical addictions involve dependence on psychoactive substances, leading to both physiological and psychological alterations. These addictions are characterized by tolerance development, withdrawal symptoms, and compulsive substance-seeking behaviors (15).

Alcohol addiction is among the most prevalent forms of substance addiction, posing significant health risks such as liver cirrhosis, hypertension, and cognitive impairments. Additionally, it disrupts social relationships and contributes to workplace inefficiencies. Similarly, nicotine addiction, primarily through tobacco use, is associated with heightened risks of lung cancer and cardiovascular diseases, emphasizing its broader implications for public health. Illicit drug addiction, including opioids, amphetamines, and cocaine, profoundly impacts brain chemistry, reinforcing addictive behaviors and complicating treatment efforts (16).

The misuse of prescription medications, particularly opioids and benzodiazepines, constitutes a growing public health concern. These substances, while medically beneficial, pose a high risk for dependency when misused, often leading to cognitive impairments and overdose fatalities (17).

Behavioral Addictions (Process Addictions)

Behavioral addictions, also referred to as process addictions, involve compulsive engagement in non-substance-related activities, which can be equally disruptive to individuals' well-being. Technology addiction, particularly excessive internet and social media use is increasingly recognized as a significant behavioral disorder. It adversely affects academic performance, interpersonal relationships, and sleep patterns. Similarly, gaming addiction, a subset of technology addiction, is linked to reduced physical activity and mental health issues, especially among adolescents (18). Gambling addiction leads to severe financial and psychological consequences, often resulting in debt accumulation, strained relationships, and heightened stress levels. Shopping addiction exhibits similar compulsive patterns, causing financial instability and emotional distress (19). Food addiction, characterized by the excessive consumption of highly processed and calorie-dense foods, contributes to obesity, diabetes, and cardiovascular disorders. Emotional triggers such as stress and anxiety often exacerbate this form of addiction (20).

Both chemical and behavioral addictions exert profound effects on individuals and societies. Understanding the nuances of each type is essential for developing effective prevention, treatment, and rehabilitation strategies. Addressing addiction from a public health perspective underscores the necessity for comprehensive intervention models encompassing biological, psychological, and socio-environmental factors (21).

Table 1. Neuroanatomical structures involved in addiction

Neuroanatomical structure	Function in addiction
Ventral tegmental area (VTA)	• The VTA plays a central role in addiction by producing dopamine, a neurotransmitter crucial for reward processing. Substance use or addictive behaviors increase dopamine release from the VTA, reinforcing addiction
Nucleus accumbens	• The nucleus accumbens is central to the brain's reward system and responds to dopamine release, creating pleasure and reinforcing addictive behavior
Prefrontal cortex	• Responsible for decision-making, impulse control, and self-regulation. Chronic addiction impairs prefrontal cortex function, weakening an individual's ability to resist addictive urges
Amygdala and hippocampus	• The amygdala regulates emotional responses related to addiction, while the hippocampus stores addiction-related experiences in memory, increasing the likelihood of seeking addictive substances or behaviors

Table 2. Neurotransmitters involved in addiction

Neurotransmitter	Role in addiction
Dopamine	• Regulates reward and pleasure responses. Addictive substances and behaviors significantly increase dopamine levels, reinforcing addictive behaviors. Over time, the dopamine system becomes desensitized, requiring higher doses to achieve the same effect (tolerance)
Serotonin	• Involved in mood regulation, sleep, and appetite. Altered serotonin levels contribute to addiction-related behaviors, such as compulsive eating
Glutamate	• Plays a role in learning and memory, essential for reinforcing addiction-related habits
GABA	• A calming neurotransmitter, affected by substances such as alcohol and sedatives, leading to dependency

GABA: Gamma-amino butyric acid

Neuroanatomy, Physiology, and Mechanisms of Addiction

Addiction not only affects an individual's behavior and quality of life but also induces significant and long-lasting changes in brain structures and physiological processes. The development and persistence of addiction are closely related to the brain's reward system, neurotransmitters, and dysfunctions in neural circuits (22). Below, the neuroanatomical and physiological foundations of addiction are examined in detail.

Neuroanatomical Structures

Addiction primarily involves the brain's reward system and its associated regions. This system regulates feelings of pleasure and motivation, forming the basis of addictive behaviors. The key neuroanatomical structures implicated in addiction are detailed in Table 1 (22).

Neurotransmitters

Neurotransmitters, particularly dopamine and serotonin, play a critical role in addiction development and maintenance. Table 2 presents the major neurotransmitters involved in addiction and their functions (23).

Physiological Processes

Addiction triggers a series of physiological changes in the brain, explaining its chronic nature and the difficulties in treatment. One of the primary physiological changes is the development of tolerance, which occurs when repeated exposure to an addictive substance or behavior causes the brain's reward system to become desensitized. This results in the need for increasingly higher doses to achieve the same effect. When an individual ceases or reduces their substance use, withdrawal symptoms emerge, characterized by both physical and psychological distress. These symptoms often include anxiety, depression, sweating, tremors, and insomnia, further reinforcing the cycle of addiction. Additionally, chronic addiction leads to structural and functional changes in the brain's neural connections, a phenomenon known as neuroplasticity. These changes make addiction a deeply ingrained behavior that becomes progressively harder to overcome (22).

Mechanisms of Addiction

Addiction disrupts the balance between the brain's reward-motivation system and cognitive control processes. This process follows a cycle. The process begins with reward activation, where addictive substances or behaviors lead to excessive dopamine release, creating an intense sense of pleasure. Over time, compulsive seeking emerges as the natural reward system becomes less responsive, causing individuals to derive less satisfaction from non-addictive activities (24). As addiction, progresses, cognitive control impairment occurs due to dysfunction in the prefrontal cortex, making it increasingly difficult for individuals to resist addictive impulses. Finally, stress and relapse play a crucial role in perpetuating addiction, as heightened stress responses and elevated cortisol levels significantly increase the risk of returning to addictive behaviors. Understanding these mechanisms is crucial for developing effective treatments that target both biological and behavioral aspects of addiction (25).

Causes and Symptoms of Addiction

Addiction results from an interplay of genetic predisposition, environmental conditions, and psychological factors. The likelihood of addiction development and its progression are shaped by biological, emotional, and social influences (26,27).

Risk Factors for Addiction

The primary risk factors contributing to addiction include biological, psychological, and environmental determinants (26,27).

Genetic Factors: Studies indicate that addiction has a genetic basis, with individuals having a family history of addiction being at a higher risk. Variations in dopamine receptor genes influence reward processing, increasing susceptibility to addiction. Twin and adoption studies estimate that genetic factors contribute approximately 40-60% to addiction risk (28).

Psychological Factors**:** Psychological stressors, including trauma, depression, anxiety, and low self-esteem, significantly increase addiction risk. Addiction often serves as a maladaptive coping mechanism for regulating emotions. For example, alcohol or drugs may temporarily alleviate anxiety but ultimately lead to dependency (29).

Environmental Factors: Socioeconomic status, education level, peer influence, and early exposure to addictive substances are key environmental risk factors. Adolescence is particularly critical, as early exposure increases the likelihood of developing addiction in adulthood (28).

Symptoms of Addiction: Addiction manifests through physical, emotional, and social symptoms. The severity and progression of these symptoms vary based on the individual and type of addiction (30).

Physical Symptoms: Individuals experiencing addiction often develop tolerance, requiring higher doses of the substance to achieve the same effect. Withdrawal symptoms, which occur when the substance is discontinued, may lead to significant physical discomfort. Furthermore, addiction-related health issues, such as liver damage from alcohol, respiratory diseases from tobacco, and neurological impairments from stimulant use, can arise as the condition progresses (31).

Emotional Symptoms: Addiction is frequently accompanied by mood swings, alternating between euphoria and depressive states. Additionally, individuals may experience

Table 3. DSM-5 criteria for substance use disorders

To diagnose substance use disorder, at least two of the following 11 criteria must be met within a 12-month period*
1. Uncontrolled substance use: The substance is often used for longer periods or in larger amounts than intended
2. Unsuccessful attempts to cut down or quit: Persistent efforts to reduce or control substance use fail
3. Excessive time spent on substance-related activities: A significant amount of time is dedicated to obtaining, using, or recovering from substance effects
4. Strong cravings: A powerful urge or desire to use the substance
5. Failure to fulfill major obligations: Continued use results in the inability to meet responsibilities at work, school, or home
6. Persistent use despite social or interpersonal problems: Continued substance use despite relationship or social problems caused by its effects
7. Withdrawal from important activities: Social, occupational, or recreational activities are reduced or abandoned due to substance use
8. Use in hazardous situations: The substance is used in physically dangerous circumstances (e.g., driving under the influence)
9. Continued use despite physical or psychological harm: Continued use despite awareness of the substance causing or worsening health problems
10. Tolerance development: a. The need for increasing amounts of the substance to achieve the same effect b. Reduced effect when using the same amount
11. Withdrawal symptoms: a. The emergence of specific withdrawal symptoms when substance use is stopped b. Continued use of the substance to relieve withdrawal symptoms
*: After diagnosis, the severity of the disorder is classified as follows: • Mild: 2-3 criteria met • Moderate: 4-5 criteria met • Severe: 6 or more criteria met
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, fifth edition

a loss of interest in previously enjoyable activities, as their focus becomes centered on the addictive substance or behavior (32).

Social Symptoms: Social withdrawal is common among individuals with addiction, leading to reduced engagement in relationships and social activities. The consequences of addiction often extend to the workplace or educational settings, resulting in decreased performance and, in severe cases, job loss or school dropout. Additionally, family relationships may become strained due to conflicts arising from addictive behaviors (33).

Addressing addiction requires a multifaceted approach, integrating biological, psychological, and social factors. Understanding these risk factors and symptoms is essential for prevention and treatment (34).

Diagnostic Criteria and Evaluation of Addiction

The diagnosis and evaluation of addiction involve a systematic analysis of the physical, psychological, and social symptoms associated with substance use or behavioral dependence. International classification systems, clinical assessment methods, and biological tests serve as crucial tools in this process (35).

Diagnostic Criteria for Addiction

The most widely used systems for diagnosing addiction are the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) and the International Classification of Diseases, tenth edition (ICD-10). DSM-5 categorizes addiction under "substance use disorders", evaluating it based on 11 criteria. These criteria classify addiction as mild, moderate, or severe, depending on the number of symptoms present. DSM-5 distinguishes between "substance use disorders" and "substance-induced disorders" (36). The diagnostic criteria in DSM-5 for substance use disorders require at least two of the following symptoms within a 12-month period: impaired control over substance use, unsuccessful attempts to reduce or quit, excessive time spent obtaining or using the substance, strong cravings, failure to fulfill major obligations, continued use despite social or interpersonal problems, reduced participation in important activities, use in physically hazardous situations, persistent use despite awareness of physical or psychological harm, tolerance development, and withdrawal symptoms (35). Table 3 presents the DSM-5 criteria for substance use disorders.

The ICD-10, in contrast, defines addiction under "substance dependence syndrome" using six main criteria: a strong desire to use the substance, difficulties in controlling use, withdrawal symptoms, tolerance development, neglect of other activities due to substance use, and continued use despite harmful consequences. The focus of the ICD-10 criteria is to assess whether substance use leads to significant impairment in an individual's life functions. Diagnosing addiction accurately is critical for designing effective treatment strategies (36).

Evaluation of Addiction

The assessment of addiction relies on clinical interviews, standardized questionnaires, and biological tests. Clinical interviews are conducted in structured or semi-structured formats to identify addiction-related symptoms, substance use patterns, and motivational levels. Questionnaires and scales are employed to evaluate substance consumption, addiction severity, and behavioral consequences. Commonly used assessment tools include the addiction severity index and the Alcohol Use Disorders Identification Test (37). Self-report questionnaires also play an essential role, allowing individuals to provide insights into their substance use habits and psychological states. Biological tests offer objective methods to detect substance use and measure addiction severity. Blood tests are used to identify the presence and concentration of addictive substances, while liver enzyme tests help assess long-term alcohol use. Urine tests are widely utilized for detecting recent drug consumption due to their low cost and efficiency. Saliva tests provide short-term detection of substance use, whereas hair tests offer an extended history of substance consumption, tracing usage over several months. A comprehensive evaluation of addiction requires integrating these diagnostic criteria and assessment methods to formulate an individualized treatment plan (38).

Organizations Responsible for Combating Addiction

The fight against addiction requires collaboration between national and international institutions that focus on prevention, treatment, and rehabilitation. In Türkiye and worldwide, various governmental agencies, non-governmental organizations, and research centers play crucial roles in addressing addiction (39).

Institutions and Organizations Combating Addiction in Türkiye

Turkish Green Crescent Society (*Yeşilay*)

Founded in 1920, *Yeşilay* works to combat addictions related to alcohol, tobacco, drugs, technology, and gambling. The organization conducts public awareness campaigns, educational programs, and counseling services through the Green Crescent Counseling Centers (*Yeşilay Danışmanlık Merkezi*), which provide psychological and social support for individuals struggling with addiction. Yeşilay also implements school-based prevention programs to educate youth on addiction risk (40).

AMATEM *(Alkol ve Uyuşturucu Madde Bağımlıları Tedavi ve Araştırma Merkezi)*

AMATEM facilities, operating under the Turkish Ministry of Health, specialize in the medical treatment of substance and alcohol addiction. These centers offer detoxification, pharmacological treatment, psychotherapy, and rehabilitation services. AMATEM plays a pivotal role in addressing addiction-related health concerns and providing structured recovery programs (40).

Social Adaptation and Support Centers [*Sosyal Uyum Destek Merkezi* (SUDEM)]

Established by the İstanbul Metropolitan Municipality, SUDEM focuses on the reintegration of individuals recovering from addiction. These centers provide psychological counseling, rehabilitation programs, and social adaptation support. SUDEM professionals, including psychologists, occupational therapists, and social workers, collaborate to offer a holistic approach to addiction recovery.

Turkish Monitoring Center for Drugs and Drug Addiction [*Türkiye Uyuşturucu ve Uyuşturucu Bağımlılığı İzleme Merkezi* (TUBİM)]

TUBİM, affiliated with the Turkish National Police, is responsible for monitoring drug-related activities and formulating policies for drug control. The center collects and analyzes data on drug use, trafficking, and addiction trends in Türkiye, contributing to evidence-based policy-making (41).

Universities and Research Institutions

Academic institutions conduct scientific research on addiction, contributing to the development of effective treatment and prevention strategies. Universities also provide education and training in psychology, medicine, and social work to equip professionals with the necessary skills to address addiction-related challenges (42).

International Organizations Combatting Addiction

World Health Organization (WHO)

WHO develops international policies and strategies to combat addiction, providing guidelines on prevention, treatment, and rehabilitation. It also collects and analyzes global data on substance use and addiction-related health impacts (43).

United Nations Office on Drugs and Crime (UNODC)

UNODC coordinates global efforts to prevent drug trafficking and addiction. It implements drug control policies, supports treatment programs, and collaborates with governments to combat illicit drug trade. UNODC works to reduce both the supply and demand of addictive substances (44).

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)

EMCDDA monitors drug use and addiction trends in European countries, providing evidence-based recommendations for policy development. The organization publishes annual reports on substance use and promotes best practices in addiction prevention and treatment (45). Updated the institutional name from EMCDDA to European Union Drugs Agency (EUDA), effective from 2 July 2024.

National Institute on Alcohol Abuse and Alcoholism (NIAAA) and National Institute on Drug Abuse (NIDA)

In the United States, NIAAA focuses on alcohol addiction research, while NIDA conducts studies on drug dependency. These institutions support the development of new treatment approaches and public health initiatives (46).

Global Cooperation and Networks

International collaboration is essential in addressing the global challenge of addiction. Organizations such as WHO, UNODC, and EMCDDA facilitate cross-border cooperation, data sharing, and policy development to mitigate the impact of addiction worldwide (47).

Türkiye and the international community recognize that addiction is not just an individual issue but also a broader public health concern. The efforts of these institutions emphasize the necessity of multidisciplinary collaboration to prevent addiction, provide effective treatment, and support long-term recovery (48).

Conclusion

Addiction is a complex issue that extends beyond individual struggles, affecting societies and public health on a global scale. Throughout history, its understanding and regulation have evolved, emphasizing the interplay of biological, psychological, and environmental factors. Today, both substance and behavioral addictions require scientifically grounded diagnosis and treatment approaches, supported by national and international institutions. Effective prevention and rehabilitation efforts depend on a holistic approach that integrates medical, psychological, and social interventions. Addressing addiction with a comprehensive perspective is essential to reducing stigma, improving recovery outcomes, and fostering long-term well-being.

Footnotes

Authorship Contributions

Concept: G.Z.Y., M.T., Design: G.Z.Y., M.T., Analysis or Interpretation: G.Z.Y., M.T., Literature Search: G.Z.Y., M.T., Writing: G.Z.Y.

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