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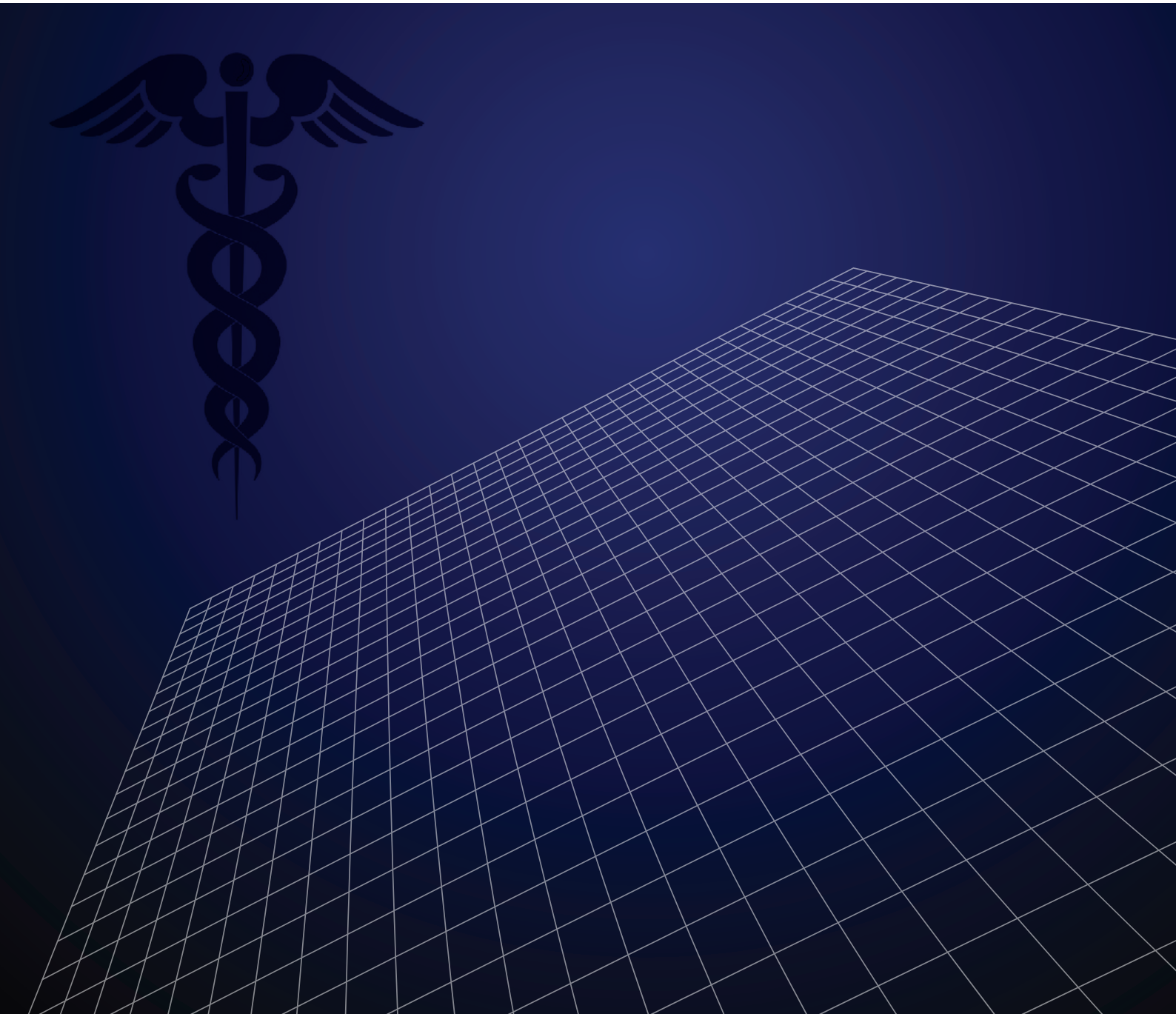

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INDEX

İÇİNDEKİLER

ARAŞTIRMA MAKALE / RESEARCH ARTICLE

INDEX
İÇİNDEKİLER

INDEX

İÇİNDEKİLER

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Research Article

Hypertension and insulin resistance in rheumatoid arthritis: unveiling insights with mets-ir index

METS-IR indeksi perspektifinden romatoid artritte hipertansiyon ve insülin direnci

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Abstract

Aim: Hypertension (HT), together with metabolic dysfunctions and insulin resistance (IR) in its pathophysiology, is a significant risk factor for cardiovascular disease in rheumatoid arthritis (RA) patients. Identifying IR early could enhance HT management, especially in RA patients, where HT prevalence is elevated. The study aimed to assess metabolic indices, particularly the METS-IR, as predictors of HT in RA patients.

Material and Methods: This retrospective, cross-sectional study investigated the association between RA, IR, and HT in 80 RA patients and 80 age- and sex-matched controls. Patients with diabetes, pre-diabetes, or other conditions affecting insulin sensitivity were excluded, as were those on glucose-metabolism-affecting medications except low-dose glucocorticoids (<7.5 mg/day prednisone or equivalent).

Results: RA patients exhibited significantly higher HT prevalence than controls (65% vs. 22.5%; p=0.044). HOMA-IR and METS-IR scores were significantly higher in RA patients (p=0.04 and p=0.01, respectively), while QUICKI scores were significantly lower (p=0.04). Glucocorticoid use didn't affect METS-IR, HOMA-IR, or QUICKI scores. Hypertensive patients had significantly higher HOMA-IR and METS-IR scores (p=0.009 and p<0.001, respectively), with both showing a significant association with HT in multivariate analyses (p=0.002 for both). Age emerged as a significant factor in the development of HT, with each passing year increasing the likelihood by 7% (p=0.042).

Conclusion: HT was more prevalent in RA patients, with higher METS-IR levels irrespective of glucocorticoid use or disease activity. Each unit increase in METS-IR score correlated with a 15% higher HT risk. METS-IR could serve as an early prediction tool for HT in RA.

Keywords: METS-IR, Rheumatoid arthritis, Hypertension, Insulin resistance, HOMA-IR, Metabolic Indices.

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Öz

Amaç: Hipertansiyon (HT), patofizyolojisindeki metabolik disfonksiyon ve insülin direnciyle birlikte, RA hastalarında önemli bir kardiyovasküler hastalık risk faktörüdür. Bu nedenle, özellikle RA gibi HT sıklığının arttığı hastalarda, insülin direncinin erken saptanması önemlidir. Çalışmamız, ön planda METS-IR olmak üzere, metabolik indekslerin, RA hastalarında HT öngörü değerini araştırmayı amaçlamıştır.

Gereç ve Yöntemler: Bu retrospektif, kesitsel çalışmaya 80 RA hastası ile yaş ve cinsiyet açısından eşleştirilmiş 80 sağlıklı kontrol dahil edilmiştir. Diyabet, prediyabet veya insülin duyarlılığını etkileyen hastalıklar ile düşük doz glukokortikoidler dışında (<7.5 mg/gün prednizon veya eşdeğeri) glukoz metabolizmasını etkileyen ilaç kullanımı olanlar dışlanmıştır.

Bulgular: RA hastalarında HT sıklığı kontrol grubuna göre anlamlı derecede yüksekti (sırasıyla %65 ve %22.5; p=0.044). HOMA-IR ve METS-IR skorları yine RA grubunda, anlamlı derecede yüksekken (sırasıyla p=0.04 ve p=0.01), QUICKI skorları anlamlı derecede düşüktü (p= 0.04). Glukokortikoid maruziyetinin METS-IR, HOMA-IR veya QUICKI skorlarına etkisi olmadığı izlendi (sırasıyla p=0.410, p=0.583 ve p=0.583). Hipertansif hastaların ortalama HOMA-IR ve METS-IR skorları, hipertansif olmayanlara kıyasla anlamlı derecede yüksekti (sırasıyla p=0.009 ve p<0.001). Çok değişkenli analizlerde, HT ile hem HOMA-IR hem de METS-IR indeksleri anlamlı bir ilişki gösterdi (p=0.002 her ikisi için). Yaşın HT gelişimi üzerinde önemli bir faktör olduğu, yıllık %7 risk artışına yol açtığı gözlenmiştir (p=0.042).

Sonuç: Çalışmamızda HT sıklığının RA hastalarında anlamlı derecede yüksek olduğu ve glukokortikoid kullanımı veya hastalık aktivite durumundan bağımsız olarak METS-IR skorlarının anlamı derecede yüksek olduğunu gösterilmiştir. METS-IR skorunda meydana gelen her bir birimlik artış, RA hastalarında HT gelişme riskinde %15'lik bir artışa neden olmaktadır. METS-IR, bu açıdan HT için pratik bir öngörü aracı olabilir.

Anahtar Kelimeler: METS-IR, Romatoid artrit, Hipertansiyon, İnsülin direnci, HOMA-IR, Metabolik indeksler.

Introduction

Rheumatoid arthritis (RA) is a systemic, inflammatory and chronic autoimmune disorder that leads to symmetrical polyarthritis involving both small and large joints, predominantly occurring between the ages of 30 and 50 years. Globally, approximately 1% of the population is diagnosed with RA, which not only diminishes quality of life but also increases the mortality risk due to various comorbidities, particularly cardiovascular (CV) diseases. Studies show that RA patients have a 1.5 times higher risk of CV comorbidities than the general population, with CV diseases leading as the primary cause of death and accounting for 39% of all mortalities in these patients. Furthermore, individuals with RA are at 48% greater risk of experiencing CV events than those without RA (1, 2).

Among CV risk factors, hypertension (HT) is notably prevalent and potent in patients with RA. This was the strongest modifiable risk factor for CV disease in this group. A review of insurance claims in the United States revealed that 76% of RA patients were diagnosed with HT, nearly double the incidence in matched controls. This higher prevalence is consistent across the Canadian and European populations, highlighting the global relevance of HT in RA. Moreover, the incidence of HT in patients with RA is notably higher than that in the general population, with a significant incidence rate difference highlighted in the UK-based medical records (3, 4).

The link between RA and increased HT risk is complex and may involve multiple factors, including systemic inflammation, obesity, sedentary lifestyle, dietary habits, and RA medication. Understanding these relationships is crucial for managing HT in patients with RA and subsequently reducing the risk of future CV disease (5).

Further complicating the landscape of risk assessment in patients with RA is the association between HT and insulin resistance (IR) and metabolic syndrome (MS), both of which contribute to arterial stiffness and elevated CV risk. HOMA-IR (homeostatic model assessment of insulin resistance) and QUICKI (quantitative insulin sensitivity check index) indices calculate insulin resistance using fasting serum insulin and glucose levels. Meanwhile, the metabolic score for insulin resistance (METS-IR) index is a novel, non-insulin-based measure that also holds potential as a valuable predictor of HT and might provide a practical, efficient and more economical screening

tool for metabolic dysfunction according to recent studies (6-8).

In this study, to improve the early prediction and management of HT in patients diagnosed with RA, we aimed to determine the predictive value of the METS-IR index for incident HT particularly in RA patients with supporting the results with HOMA-IR and QUICKI scores.

Material and Methods

Patient Selection and Ethical Considerations

This retrospective cross-sectional multicenter study was conducted in accordance with the Declaration of Helsinki and approved by the Adana City Training and Research Hospital Clinical Research Ethics Committee with decision number 3201 at February 29, 2024).

Inclusion Criteria

Patients were selected from sequential visitors from rheumatology and physical medicine and rehabilitation outpatient clinics for routine checkup and the study only included patients diagnosed with RA based on the European Alliance of Associations for Rheumatology (formerly known as European League Against Rheumatism)/American College of Rheumatology (ACR) 2010 classification criteria for rheumatoid arthritis.

Exclusion Criteria

Exclusion criteria included patients with an HbA1c level of 5.5% or above, indicating the presence of diabetes or pre-diabetes, which could confound the relationship between RA and insulin resistance. Also, patients with comorbid conditions that could independently affect insulin sensitivity, such as thyroid disorders, Cushing's syndrome, or polycystic ovary syndrome (PCOS) were also excluded. Additionally, patients with concomitant renal, hepatic, cardiac or endocrine diseases or taking medications affecting lipid metabolism and glucose metabolism (except low dose glucocorticoids) were excluded from the study. Additonally, patients exhibiting a high disease activity level, as indicated by a disease activity score of 28 joints (DAS28) greater than 5.1 were excluded regarding the fact that acute inflammation may effect metabolic parameters.

The low-dose glucocorticoids (defined as <7.5 mg/day prednisone or equivalent) use were not exception in order to not disrupt the routine maintenance treatment. Patients treated with the higher dose of 7.5 mg/day prednisone or equivalent doses were excluded.

Data Collection

Demographic data, including age, gender and body mass index and clinical data, including HbA1c, serum glucose, serum insulin, triglycerides and high density lipoprotein (HDL) measured after an overnight fasting, were collected retrospectively. Data on HT were incorporated into the dataset from the examination notes established during the clinical assessments or from the existing diagnosis of HT. HT defined as being previously diagnosed with HT and/or being under antihypertensive treatment, or newly detected and confirmed by appropriate consecutive measurements of ≥140 mmHg systolic and/or ≥90 mmHg diastolic blood pressure during examination according to the WHO 2021 HT guideline (9). HOMA-IR was calculated according to the formula: fasting insulin (microU/L) x fasting glucose (mmol/L)/22.5. METS-IR was calculated using the following formula: ln[(2 × fasting plasma glucose (mg/dL) + fasting triglyceride (mg/dL)] × body mass index (kg/m2)/(ln[high-density lipoprotein cholesterol (mg/dL)]).

Statistical Analysis

The data were analyzed with IBM SPSS Statistics software (version 22, IBM Corp., Armonk, N.Y., USA). Descriptive statistics covered demographic and clinical features. Categorical variables were described with frequency counts and percentages, analyzed with cross-tabulations and Yates' continuity correction. For numerical variables, either mean ± standard deviation (for normal distribution) or median with minimum-maximum ranges (for non-normal distribution) were presented. Normality was tested using Kolmogorov-Smirnov or Shapiro-Wilk tests. Based on distribution, independent sample t-tests and Mann-Whitney U tests were used for two independent groups, while Kruskal-Wallis H tests or One-way ANOVA were used for more than two groups. Statistical significance was set at $p < 0.05$, with interpretations reported as $p < 0.05$, $p < 0.01$, or $p < 0.001$. Univariate and multivariate logistic regression analyses assessed factors influencing HT presence in RA patients, calculating odds ratios (ORs) and 95% confidence intervals (CIs) for risk assessment.

Results

This study evaluated a cohort of 80 patients diagnosed with RA along with a control group of 80 age and sex-matched individuals. All participants were classified as nondiabetic with HbA1c levels < 5.5%. The general demographic characteristics of the RA and control groups are presented in Table 1.

Table 1. Demographic data and comparison of hypertension and metabolic indices between control and patient groups

	Control (n=80)	RA (n=80)	p
Age	50.06 ± 10.375	51.69 ± 8.857	0.062
Gender			0.661
Female	68 (85%)	71 (87.75%)	
Male	12 (15%)	9 (11.25%)	
BMI	27.109 ± 4.845	27.25 ± 4.296	0.876
HT			
No	62 (77.5%)	28 (35%)	0.044*
Yes	18 (22.5%)	52 (65%)	
Disease Duration		6 (1-15) years	
DAS 28		3.1 (2.1-5.2)	
CRP		5,5 (0.1-10.2)	
HOMA-IR	1.2 (0.2–6.1)	1.8 (0.8–4.8)	0.04*
QUICKI	0.4 (0.3–0.5)	0.3 (0.2–0.4)	0.04*
METS-IR	37.7 (22.4–122.62)	39.9 (28.3–32.6)	0.01*

* $p < 0.05$
Values within parentheses represent minimum and maximum values
RA: Rheumatoid Arthritis, BMI: Body Mass Index, HT: Hypertension, DAS28:(Disease Activity Score 28), CRP: C-Reactive Protein, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, QUICKI: Quantitative Insulin Sensitivity Check Index, METS-IR: Metabolic Score for Insulin Resistance

Patients with RA showed significantly higher HT prevalence compared to control group (65% vs. 22.5%, p= 0.044). The metabolic indices HOMA-IR (p = 0.04) and METS-IR (p = 0.01) were also significantly higher in patients with RA and as expected, QUICKI (p = 0.04) (was significantly lower in the RA group. (Table 1).

To assess the effect of glucocorticoid therapy on metabolic indices in patients with RA, a comparative analysis was performed between patients who did not use glucocorticoids (n=26) and those who received low-dose glucocorticoid therapy (n=54). The median age of patients in the low-dose glucocorticoid group was slightly higher comparing patients not using glucocorticoids (59 vs. 51.5, respectively, p=0.04). METS-IR scores were 40.8 (range 28.5-54.7) for those not on glucocorticoids compared to 39 (range 28-59.6) for those on low-dose glucocorticoids. HOMA-IR values were 1.5 (range 0.7-3.5) for those not on glucocorticoids compared to 1.5 (range 0.4-4.8) for those on low-dose glucocorticoids. QUICKI scores were 0.4 (range 0.2-0.4) for non-glucocorticoid users and 0.4 (range 0.2-0.4) for low-dose glucocorticoid users. Neither of these differences in metabolic indices reached statistical significance (p= 0.410 for METS-IR, p= 0.583 for HOMA-IR and p= 0.583 for QUICKI).

To assess the influence of disease activity on metabolic indices in patients with RA, a comparative analysis was performed between patient groups categorized by disease activity levels: remission, low-disease activity and moderate-disease activity, as defined by the Disease Activity Score in 28 joints (DAS28). The HOMA-IR values were as follows: for the remission group the value was 1.6 (range 0.7 -4.8), for the low disease activity group was 1.7 (range 0.8 -3.3) and for the moderate disease activity group was 1.4 (range 0.5 - 4.0). The QUICKI values for the remission group was 0,4, for the low disease activity group the value was 0,4 and for the moderate disease activity group the value was 0,36. The METS-IR values for the remission group was 40,2, for the low disease activity group was 39,9 and for the moderate disease activity group was 39,8. There were no statistically significant differences between the DAS28 groups (p = 0.6 for HOMA-IR, p = 0.6 for QUICKI and p = 0.8 for METS-IR).

Comparative analysis of metabolic indices between RA patients with and without HT revealed statistically significant differences. The average METS-IR and HOMA-IR scores, indicatives of insulin resistance, were higher in hypertensive patients compared to non-hypertensive counterparts. (44.9 vs. 36.7, p<0,001 for METS-IR and 1.7 vs. 1.3, p= 0.009 for HOMA-IR, respectively) (Table 2).

Table 2. Comparison of metabolic indices in RA patients with and without hypertension

	HT		
	No	Yes	p
HOMA-IR	1.3 (0.2–6.1)	1.7 (0.4–4.3)	0.009*
QUICKI	0.4 (0.2–0.4)	0.3 (0.3–0.5)	0.059
METS-IR	36.7 (22.3–53.5)	44.9 (30.0–122.6)	<0.001**

* $p < 0.05$; ** $p < 0.001$
Values within parentheses represent minimum and maximum values
HT: Hypertension, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, QUICKI: Quantitative Insulin Sensitivity Check Index, METS-IR: Metabolic Score for Insulin Resistance

Univariate analysis showed that age was a significant factor of HT, with each year increasing the odds by 7% (OR 1.07, 95% CI 1.02-1.12, p = 0.006). This relationship remained significant in the multivariate model (OR 1.059, 95% CI 1.002-1.12, p = 0.042). HOMA-IR and METS-IR were both significantly associated with HT in the univariate model, with ORs of 1.10 (p < 0.001) and 1.15 (p < 0.001), respectively. These relationships of HOMA-IR and METS-IR also remained significance in the multivariate analyses (OR 1.10 and 1.13, p=0,002 for both, respectively) (Table 3).

Table 3. Logistic regression analysis of factors associated with hypertension in RA patients

	Univariate Logistic Regression		Multivariate Logistic Regression	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.07(1.02-1.12)	0.006**	1.059 (1.002-1.12)	0.042*
HOMA-IR	1.10 (0.91-1.33)	<0.001***	1.10 (0.92-1.21)	0.002**
QUICKI	0.00 (0-20.29)	0.121		
METS-IR	1.15 (1.07-1.23)	<0.001***	1.13 (1.05-1.21)	0.002**

OR: Odds Ratio; CI: Confidence Interval; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Values within parentheses represent minimum and maximum values
HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, QUICKI: Quantitative Insulin Sensitivity Check Index, METS-IR: Metabolic Score for Insulin Resistance

Discussion

The use of metabolic indices to gauge insulin resistance, a known risk factor for HT, has emerged as a practical approach in clinical practice (10). These indices serve not only as tools for the early detection of metabolic dysfunctions that precede HT but also help stratify patients according to their CV risk (6). One of these indices, METS-IR, designed as a practical surrogate of insulin resistance based on BMI, fasting plasma glucose, high-density lipoprotein and triglyceride levels. While the strong association of METS-IR score with increased frequency of HT, CV events and mortality was shown by several studies (5,7,8,11,12), our study is the first to extends this understanding to patients with RA, underscoring the importance of these indices in predicting CV complications, such as HT.

As declared by several studies, insulin resistance, a well-known risk factor for CV disease, appears to be exacerbated by the systemic inflammatory state induced by RA, potentially through mechanisms involving cytokine-mediated interference in insulin signaling pathways (11,13,14).

Consistent with the literature, the prevalence of HT, HOMA-IR and METS-IR scores were significantly higher while, as expected, QUICKI score was significantly lower in our RA group comparing healthy controls. These findings suggest that insulin resistance is more prominent in patients with RA comparing general population. The increase in METS-IR and its association with HT observed in our study are particularly noteworthy. There was a clear association between HT and elevated metabolic indices in RA patients, as evidenced by higher scores of HOMA-IR and METS-IR in hypertensive patients than in their non-hypertensive counterparts. This correlation supports the hypothesis that systemic inflammation observed in RA may exacerbate insulin resistance, thereby contributing to an increased risk of HT.

Compared with existing studies, Han et al. found a strong correlation between elevated METS-IR levels and CV events in the general population, which aligns with our findings in the RA cohort (7). This suggests that metabolic dysfunction, as measured by METS-IR, may be a critical and specific indicator of HT risk not only in the general population but also in patients with RA who are already at increased CV risk. The consistent observation across various studies that RA patients exhibit worse metabolic profiles than controls could reflect an underlying link between active inflammatory pathways in RA and metabolic disturbances. This connection underscores the need for comprehensive approaches that address both inflammation and metabolic health to HT risk in patients with RA (12,16,17).

The logistic regression analyses presented in our study indicated that specific increments in metabolic indices significantly elevate the risk of developing HT in patients with RA. The ORs derived from both univariate and multivariate logistic regression models suggested a direct relationship between these metabolic scores and HT risk. For each unit increase in METS-IR score, there was an associated 15% increase in the likelihood of HT. This effect remained significant in the multivariate analysis, highlighting METS-IR as a robust predictor of HT in patients with RA.

Another important point of our study is while the presence of systemic inflammation due to rheumatoid arthritis was observed to increase the frequency of HT and insulin resistance compared to the control group, multivariate analyses revealed that the degree of inflammation determined by the DAS28 score did not have any effect on these variables. This important result suggests that RA can create systemic effects, such as increase in HT and insulin resistance, regardless of the inflammatory activity in the joints, even in a state of remission.

Investigating the interplay between RA disease activity, medication effects and metabolic indices could provide deeper insights into the pathophysiology of CV risk in RA and refine the risk stratification models for this patient population. The pronounced metabolic dysfunction in patients with RA might highlight the necessity of routine screening for HT and metabolic dysfunction in this group. The early identification and management of these risk factors could play a crucial role in reducing CV morbidity and mortality in patients with RA. Furthermore, the significant differences in metabolic scores between patients with RA and controls emphasize the need for tailored therapeutic strategies that address not only the inflammatory aspects of RA but also their metabolic effects.

These results suggest that clinicians should monitor these indices closely in patients with RA as part of their routine CV risk assessment and management strategies.

Limitations

The retrospective and cross-sectional nature of our study, which included a relatively low number of patients, makes it impossible for us to observe the long-term effects of insulin resistance and HT in RA patients and to examine the effects of medical treatments on these variables.

Conclusion

Our study demonstrated that HT is significantly more prevalent among patients with rheumatoid arthritis, highlighting the urgent need for targeted CV risk management in this population. The findings revealed that METS-IR and HOMA-IR levels were distinctly higher in patients with RA, establishing a clear and significant link between increased METS-IR and HOMA-IR scores and elevated risk of HT. Each unit increase in the METS-IR score corresponded to a 15% increase in the risk of developing HT in patients with RA. This relationship was consistently significant underlining the reliability of METS-IR as a predictive marker of HT in this patient population. The practical implications of our findings suggest that routine assessment of METS-IR in patients with RA could significantly enhance the predictive accuracy for HT, allowing for earlier and potentially more effective interventions. By integrating METS-IR into the standard RA management protocols, clinicians can offer a more nuanced and effective approach to managing the complex interaction of inflammation, metabolic dysfunction and CV risk in patients with RA.

Conflict of interest

The authors declare no conflict of interest. The contributions of this study are as follows:

Financial support

There is no person or organization that financially supports the study.

Prior publication

The authors declare that all or any part of the material in this work has not been published anywhere before, and is not currently under consideration for publication elsewhere. This includes symposiums, lectures, books, invited articles, submissions in electronic format and preliminary papers of all types, except abstracts of up to 400 words.

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Öz

Amaç: Sağlık ve sağlıklı yaşam hakkı, her canlının türünün devamını sağlayabilmesi için korunması gereken temel değerlerdir. Bu yaklaşım sağlık konusunun devletlerin temel sorumlulukları arasında yer almasına neden olmuştur. Sağlıklı yaşama hakkı, birçok ulusal ve uluslararası anlaşma ve sözleşmede en temel insan hakkı olarak tanımlanmış ve sağlığın korunması, insanların hastalıklarının tedavi edilmesi ve rehabilitasyonunun sağlanması görevleri devletlerin asli sorumlulukları arasına alınmıştır. İnsan Hakları Evrensel Beyannamesi'nin 25. maddesine göre sağlık hakkı, temel insan haklarından biri olarak kabul edilmiştir (İleri, Seçer ve Ertaş, 2016).

Gereç ve Yöntemler: Sağlık ikame edilemeyecek bir ihtiyaç olduğu için sunulan hizmetlerin güncel tutulması, en az sunulması kadar önemlidir. Sağlık alanında hazırlanan politikalar ve çalışmalar ile sağlığın hukuki konusunun kapsamı genişlemeye devam etmektedir. Sağlık politikaları dar anlamda sağlık hizmetlerini kapsamı alanına alırken; geniş anlamda sosyal, ekonomik, kültürel ve çevresel unsurları doğrudan veya dolaylı olarak kapsamaktadır. Bu geniş anlamda sağlık politikalarında devlet yaklaşımının ön plana çıktığı söylenebilir (Atabey, 2020). Bu nedenle 1950'lerin başında birçok OECD ülkesi sağlık sistemlerinin; politika tasarımı, planlaması, araştırması ve geliştirilmesi için doğrudan sorumluluk alan bir devlet yaklaşımını benimsemiştir. Çünkü sağlık politikası sadece sağlık hizmetlerini değil, sağlığı doğrudan veya dolaylı olarak etkileyen sosyal, ekonomik ve çevresel faktörleri de kapsamaktadır. Bu geniş kapsam nedeniyle devlet bu yaklaşımı benimsenmiş ve bu işleyiş üzerinden politikalar ve sağlık sistemleri başlatılmıştır (İleri vd., 2016).

Bulgular: Sağlık politikası, sağlık sisteminin; kurumlarını, hizmetlerini ve finansman düzenlemelerini etkileyen tüm eylemleri içermektedir. Sağlık politikası aynı zamanda, sağlık hizmetlerinin ötesinde sağlık üzerinde etkisi olan tüm kamu, özel ve gönüllü kuruluşların faaliyetlerini de içermektedir. Başka bir deyişle sağlık politikasının, sağlık hizmetlerinin sunumuna yönelik stratejiler veya yaklaşımlar oluşturan birbiriyle ilişkili kararlar ağı olduğu söylenebilir. Ayrıca sağlık politikaları, politika oluşturma sürecinin en doğru sonuca ulaşabilmesi için mevcut sağlık hizmetlerinin yanı sıra sağlığı etkileyen her türlü sosyal, ekonomik ve çevresel etkilerin de araştırılmasını gerektirmektedir (Atabey, 2020).

Sonuçlar: Bu açıklamalardan da anlaşılacağı üzere, her ne kadar hem ülkemizde hem de Dünya'nın pek çok ülkesinde biyolojik temelli sağlık politikaları ve buna dayalı hizmet sunumunun olgusal gerçekliğine rağmen, sağlık; biyolojik, psikolojik ve sosyal bileşenleri ile beraber sistemli bir bütünün çerçevesini oluşturmaktadır. Başka bir deyişle sağlık salt biyolojik bir iyilik hali olmayıp, psikolojik ve sosyal boyutları da ayrılamaz, bölünemez özelliklere sahip olup, kritik öneme haizdir. Ruh sağlığı, bireylerin zihinsel, duygusal ve sosyal iyi olma halini ifade eder. Ruh sağlığı politikaları ise toplumun ruh sağlığını koruma ve iyileştirme amacıyla geliştirilen stratejiler, yasalar ve uygulamalardır. Sosyal politika ise, toplumun genel refahını artırmayı hedefleyen, özellikle sağlık, eğitim, sosyal güvenlik ve istihdam gibi alanlarda yapılan düzenlemeler ve uygulamaları içermektedir. Genel sağlığın uzmanlık alanlarından olan ruh sağlığı alanı ise sosyal, ekonomik ve çevresel koşulları ve özellikleri ile kompakt ve simbiyotik bir ilişki içinde olup, ruh sağlığı ve ruh sağlığı hizmetlerinin bu yapısal değişkenlere yönelik duyarlılığı yüksektir. Dolayısıyla ruh sağlığı ve ruh sağlığı hizmet sunumu sosyal politikanın fonksiyonları ve araçları ile simbiyotik bir ilişki içinde olup, bu ilişkinin varlığı zorunlu bir sonuçtur.

Anahtar Kelimeler: Ruh sağlığı, Ruh sağlığı politikaları, Sosyal politika

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Abstract

Aim: The right to health and healthy life are fundamental values that must be protected in order for every living thing to survive. This approach has caused the issue of health to be among the basic responsibilities of states. The right to a healthy life is defined as the most fundamental human right in many national and international agreements and conventions, and the duties of protecting health, treating people's diseases and ensuring rehabilitation are among the primary responsibilities of states. According to Article 25 of the Universal Declaration of Human Rights, the right to health is accepted as one of the fundamental human rights (İleri, Seçer and Ertaş, 2016).

Material and Methods: Since health is a need that cannot be replaced, keeping the services offered up to date is as important as providing them. The scope of the legal issue of health continues to expand with the policies and studies prepared in the field of health. While health policies cover health services in a narrow sense; It covers, directly or indirectly, social, economic, cultural and environmental elements in a broad sense. In this broad sense, it can be said that the state approach comes to the fore in health policies (Atabey, 2020). For this reason, in the early 1950s, the health systems of many OECD countries; It has adopted a state approach that takes direct responsibility for policy design, planning, research and development. Because health policy covers not only health services but also social, economic and environmental factors that directly or indirectly affect health. Due to this broad scope, the state approach was adopted and policies and health systems were initiated through this process (İleri et al., 2016).

Results: Health policy, health system; It includes all actions affecting institutions, services and financing arrangements. Health policy also includes the activities of all public, private and voluntary organizations that have an impact on health beyond health services. In other words, it can be said that health policy is a network of interrelated decisions that create strategies or approaches to the delivery of health services. In addition, health policies require the investigation of all kinds of social, economic and environmental effects affecting health, as well as existing health services, in order for the policy-making process to reach the most accurate result (Atabey, 2020). As can be understood from these explanations, despite the factual reality of biologically based health policies and service provision based on these, both in our country and in many countries of the world, health; It forms the framework of a systematic whole with its biological, psychological and social components. In other words, health is not merely a biological state of well-being, but its psychological and social dimensions have inseparable and indivisible characteristics and are of critical importance.

Conclusions: Mental health refers to the mental, emotional and social well-being of individuals. Mental health policies are strategies, laws and practices developed to protect and improve the mental health of the society. Social policy, on the other hand, includes regulations and practices aimed at increasing the general welfare of the society, especially in areas such as health, education, social security and employment. The field of mental health, which is one of the specialties of general health, has a compact and symbiotic relationship with social, economic and environmental conditions and characteristics, and mental health and mental health services have a high sensitivity to these structural variables. Therefore, mental health and mental health service provision are in a symbiotic relationship with the functions and tools of social policy, and the existence of this relationship is a necessary consequence.

Keywords: Mental health, Mental health policies, Social policy

Giriş

Ruh Sağlığı

Ruh sağlığı, sağlığın ayrılmaz ve temel bir bileşenidir. Dünya Sağlık Örgütü sağlığı; "sadece hastalık ve sakatlık durumunun olmayışı değil, kişinin bedenen, ruhen ve sosyal yönden tam bir iyilik halinde olması" olarak tanımlamaktadır. Bu tanımın önemli bir anlamı ruh sağlığının, yalnızca ruhsal bozuklukların veya engellerin yokluğundan daha fazlası olduğudur. Bu tanımda sağlığın iyileştirilmesinin merkezinde üç fikir yer almaktadır: (1) Ruh sağlığı, sağlığın ayrılmaz bir parçasıdır, (2) ruh sağlığı, hastalık yokluğundan daha fazlasıdır ve (3) ruh sağlığı, fiziksel sağlık ve davranışla yakından ilişkilidir. Dünya Sağlık Örgütü ruh sağlığını ise "bireyin kendi yeteneklerinin farkına vardığı, yaşamın normal gerginlikleriyle başa çıkabildiği, üretken ve verimli bir şekilde çalışabildiği ve içinde yaşadığı topluma katkıda bulunabildiği bir iyilik hali" olarak tanımlamaktadır (World Health Organization, 2001, 2021).

Ruh sağlığı, bireyin ve toplumun iyilik hali ve etkin işlevselliği için esastır. Ruhsal hastalığın yokluğundan daha fazlasıdır, çünkü tanımda belirtilen durum ve yetilerin her biri kendi içinde bir değere sahiptir (Ruh sağlığını güçlendirme, 2020).

Toplum ruh sağlığı terimi ise bireye ve etkileşimde bulunduğu çevreye sunulan tüm koruyucu, tedavi edici ve rehabilite edici ruh sağlığı hizmetlerini ifade eden bir kavramdır. Bireylerin ruhsal sorunlarını aşmalarına ve hastalık nedeniyle kaybettikleri sosyal rollerine kavuşmalarına yardımcı olmak için yapılan tüm faaliyetler toplum ruh sağlığı hizmetlerinde yer almaktadır (Pektaş vd., 2006).

Modern tıp anlayışı insanı fiziksel, ruhsal ve sosyal yönden bir bütün olarak kabul etmektedir. Organizmayı oluşturan organlar ve sistemler insanın fiziksel yönünü; zihinsel, duygusal yetiler, olaylar karşısında hissedilen duygu ve düşünceler ruhsal yönünü; yaşadığı çevre ve toplumla ilişkileri ise sosyal yönünü oluşturmaktadır. Genel olarak bakıldığında birey, yaşamını, yaşadığı zaman diliminde ve değişen mekanlarda kendisiyle, ailesiyle, yakın çevresiyle, içinde yaşadığı toplumla ve çalıştığı işyeri ile yoğun bir etkileşim içinde sürdürmektedir. Eğer bu ilişkilere bağlı etkileşim sürecinde denge, uyum ve doyum varsa bireyin ruhsal yönden sağlıklı olduğu kabul edilir (Erci, 2009).

Ruh sağlığı; duygusal, psikolojik ve sosyal refahımızı içerir ve nasıl düşündüğümüzü, hissettiğimizi ve hareket ettiğimizi etkiler. Ayrıca stresle nasıl başa çıktığımızı, başkalarıyla nasıl ilişki kurduğumuzu ve sağlıklı seçimler yaptığımızı belirlemeye yardımcı olur. Ruh sağlığı, çocukluk ve ergenlikten yetişkinliğe kadar yaşamın her aşamasında önemlidir (Centers for Disease Control and Prevention, 2021).

Birden fazla sosyal, psikolojik ve biyolojik faktör, herhangi bir zamanda bir kişinin ruhsal sağlık düzeyini belirler. Kötü ruh sağlığı aynı zamanda hızlı sosyal değişim, stresli çalışma koşulları, cinsiyet ayrımcılığı, sosyal dışlanma, sağlıksız yaşam koşulları, fiziksel sağlıksızlık ve insan hakları ihlalleri ile ilişkilidir. İnsanları ruhsal sağlık sorunlarına karşı savunmasız kılan belirli psikolojik ve kişilik faktörleri vardır. Biyolojik riskler genetik faktörleri içerir. Şiddet ve kalıcı sosyo-ekonomik baskılar, ruh sağlığı için kabul edilen risklerdir (World Health Organization, 2021).

Ruhsal hastalıkların tek bir nedeni yoktur. Bir dizi faktör ruhsal hastalık riskine neden olabilir. Örneğin; travma veya istismar öyküsü gibi erken olumsuz yaşam deneyimleri (örneğin, çocuk istismarı, cinsel saldırı, şiddete tanık olma vb.), kanser veya diyabet gibi devam eden diğer tıbbi durumlarla ilgili deneyimler, beyindeki biyolojik faktörler veya kimyasal dengesizlikler, alkol veya uyuşturucu kullanımı, yalnızlık veya izolasyon duygularına sahip olmak vb. (Centers for Disease Control and Prevention, 2021).

Akıl sağlığı insanların; düşünme, duygularını ifade etme, birbirleriyle etkileşim kurma, geçimini sağlama ve hayattan zevk alma gibi kolektif ve bireysel yeteneklerinin temelidir. Bu temelde ruh sağlığının geliştirilmesi, korunması ve restorasyonu tüm dünyadaki bireylerin, toplulukların ve toplumların hayati bir görevi olarak kabul edilebilir (World Health Organization, 2021).

Ruh sağlığının geliştirilmesi, psikolojik iyi oluşu iyileştiren eylemleri içerir. Bu, ruhsal sağlığı destekleyen bir ortam oluşturmayı içerebilir. Temel medeni, siyasi, sosyo-ekonomik ve kültürel haklara saygı duyan ve bunları koruyan bir çevre, ruh sağlığı için esastır. Bu hakların sağladığı güvenlik ve özgürlük olmadan, yüksek düzeyde bir ruh sağlığını korumak zordur. Ruh sağlığı politikaları hem ruhsal bozukluklarla hem de ruh sağlığını destekleyen daha geniş konularla ilgilenmelidir. Ruh sağlığının teşviki, hükümet ve hükümet dışı politika ve programlarda ana akım haline getirilmelidir. Sağlık sektörünün yanı sıra eğitim, çalışma, adalet, ulaşım, çevre, barınma ve sosyal yardım sektörlerinin de dahil edilmesi esastır (World Health Organization, 2021).

Ruh Sağlığı ve Önemi

Ruh sağlığı, bireylerin genel sağlığının ayrılmaz bir parçasıdır ve yaşam kalitesini doğrudan etkiler. İyi bir ruh sağlığı, bireylerin strese karşı dayanıklı olmalarını, verimli bir şekilde çalışmalarını ve sosyal ilişkilerini sürdürebilmelerini sağlar. Ruh sağlığı bozuklukları ise bireylerin günlük yaşamlarını, iş performanslarını ve sosyal ilişkilerini olumsuz etkileyebilir.

Ruh Sağlığı Hizmetleri

Ruh sağlığı hizmetleri, diğer sağlık hizmetleri gibi koruyucu, tedavi edici ve rehabilite edici hizmetler olarak üç grupta toplanmaktadır. Ruh sağlığı hizmetleri bu şekilde ayrı ayrı sınıflandırılsa da birbirini etkileyen, geliştiren ve tamamlayan hizmetlerdir. Ruh sağlığı hizmetlerinin amaçları; yaşadığı toplumda ve çevrede bireyin mutlu, uyumlu ve başarılı olmasını sağlamak, ruhsal bozukluk ve hastalıkları önlemek, yani bireyi ve toplumu ruhsal hastalıklardan korumak ve ruhsal hastalıkları tedavi ederek bireyleri yeniden topluma kazandırmak şeklinde sıralanabilir (Köknel, 2000).

Günümüzde ruh sağlığı hizmetleri üç modelle sunulmaktadır. Bunlar; hastane temelli model, toplum temelli model ve toplum hastane denge modelidir (Songur vd., 2017).

Ruh Sağlığı Politikası

Ruh sağlığı politikaları, ruh sağlığı hizmetlerinin erişilebilirliğini artırmak, stigma ve ayrımcılığı azaltmak, ruh sağlığı bozukluklarının erken teşhis ve tedavisini sağlamak gibi amaçlarla geliştirilir.

Ruh sağlığı politikası, ülkelerin ruh sağlığı durumunu iyileştirme hedeflerini, bu hedefler arasındaki öncelikleri ve bunlara ulaşmak için ana yönergeleri içeren yazılı kamu belgesidir. Ruh sağlığı hedefleri için savunuculuk, ruh sağlığının teşviki, ruhsal bozuklukların önlenmesi ve tedavisi ve ruhsal hastalığı olan bireylerin optimum sosyal ve psikolojik işlevsellik kazanmalarına yardımcı olmak için rehabilitasyon bileşenlerini içerir (Saxena ve Sharan, 2008).

Ruh sağlığı politikaları gelecek için bir vizyon tanımlar ve bu da zihinsel bozuklukların önlenmesi, tedavisi ve rehabilitasyonu ve toplumda ruh sağlığının geliştirilmesi için kriterler oluşturmaya yardımcı olur (Turnpenny vd., 2018).

Ruh sağlığı politikaları, ruh sağlığı hizmetlerinin erişilebilirliğini artırmak, stigma ve ayrımcılığı azaltmak, ruh sağlığı bozukluklarının erken teşhis ve tedavisini sağlamak gibi amaçlarla geliştirilir. Etkili ruh sağlığı politikaları şu unsurları içermelidir.

1. Erken Müdahale ve Önleme: Ruh sağlığı bozukluklarının erken teşhisi ve tedavisi, uzun vadeli etkilerini azaltmada kritik öneme sahiptir.

2. Hizmetlere Erişim: Ruh sağlığı hizmetlerine eşit ve adil erişim sağlanması, tüm toplum kesimlerinin bu hizmetlerden yararlanabilmesini sağlar.

3. Eğitim ve Farkındalık: Toplum genelinde ruh sağlığı konusunda farkındalık yaratmak, stigma ve ayrımcılığı azaltmaya yardımcı olur.

Her ülkenin özel ihtiyaçları, sorunları, kaynak kısıtlamaları ve zorlukları olsa da ruh sağlığına ilişkin sosyal politikanın genel hedefleri ise genellikle aşağıdakilerden bazılarını veya tümünü içerir (Jenkins, 2008):

- Ruh sağlığını geliştirmek;
- Ruhsal ve nörolojik bozuklukları önlemek;
- Ruhsal hastalığı olan kişilerin sağlık ve sosyal işleyişini iyileştirmek;
- Erken teşhis, bakım, tedavi ve rehabilitasyon için uygun hizmetler sunmak;
- Ruhsal bozukluğu olan kişilerin erken ölüm oranlarını azaltmak;
- Damgalanmayı azaltmak;
- Ruhsal hastalığı olan kişilerin insan haklarını ve onurunu korumak;
- Genel sağlık hizmetlerinin psikolojik yönlerini desteklemek; insan kaynaklarının uygun şekilde geliştirilmesini sağlamak;
- Yukarıdaki amaçları desteklemek için bir araştırma programı geliştirmek.

Etkili bir ruh sağlığı politikasının bileşenleri şunları içerir (Jenkins, 2008):

1. Ulusal bileşenler:

- Ruh sağlığını geliştirmek, morbidite ve mortaliteyi azaltmak için ulusal bir stratejinin oluşturulması;
- İçişleri, adalet, eğitim, barınma ve finans kurumları dahil olmak üzere diğer devlet kurumlarıyla politika bağlantılarının kurulması;
- Ruhsal bozukluğu olan kişilerin tedavisi ve bakımına yönelik açık ve net hükümler içeren ve insan haklarını koruyan ruh sağlığı mevzuatının çıkarılması;
- İyi uygulama modellerini yaygınlaştırmak için sürdürülebilir finansman sağlanması, toplumda ruh sağlığının teşvik edilmesi ve sektörler arası bağlantılar kurulması;
- Etkili; uygulama planlarının yapılması, hesap verebilirliğin sağlanması ve yönetişim sisteminin kurulması.

2. Destekleyici altyapı bileşenleri:

- İnsan kaynakları stratejisi;
- Hasta katılımı stratejisi;
- Araştırma ve geliştirme stratejisi;
- Ruh sağlığı bilgi stratejisi.

3. Hizmet bileşenleri:

- Birincil bakım ve uzman bakımı arasındaki bağlantılar;
- İyi uygulama yönergeleri;
- Sivil toplum örgütleri, polis, cezaevleri ve sosyal sektörle irtibat;
- Okullarda, işyerlerinde ve toplumda ruh sağlığının teşviki;
- Mültecilerin ve ülke içinde yerinden edilmiş kişilerin ihtiyaçlarının ele alınması;
- Afete hazırlık.

Ruh sağlığı politikası geliştirmeye ve uygulamaya yönelik çabalar, yalnızca vatandaşların ruh sağlığını korumak ve geliştirmek için değil, aynı zamanda tanımlanmış ruhsal hastalığı olan kişilerin ihtiyaçlarını da ele almaya yönelik olmalıdır. Uygun maliyetli, uygulanabilir ve karşılanabilir müdahale örnekleri şunları içerir (World Health Organization, 2021)

- Depresyonun psikolojik olarak tedavisi ve orta ile şiddetli vakalar için antidepresan ilaçlar,
- Psikozun antipsikotik ilaçlar ve psikososyal destekle tedavisi,
- Alkollü içeceklerin vergilendirilmesi ve bulunabilirliğinin ve pazarlanmasının kısıtlanması,

- İntiharların önlenmesi,
- Çocuklarda ruhsal bozuklukların önlenmesi ve tedavisi,
- Demansın önlenmesi ve tedavisi ve
- Madde kullanım bozukluklarının tedavisi için bir dizi etkili önlem.
- Ruh sağlığını korumaya ve geliştirmeye yönelik politikalar şunları içerebilir (World Health Organization, 2021):
- Erken çocukluk müdahaleleri (örneğin; tehditlerden koruma, erken öğrenme fırsatları, duyarlı ve duygusal olarak destekleyici ve gelişimsel olarak teşvik edici etkileşimler, çocukların sağlığına ve beslenme ihtiyaçlarına duyarlı ve istikrarlı bir ortam sağlamak);
- Çocuklara destek (örneğin; yaşam becerileri programları, çocuk ve gençlik geliştirme programları);
- Kadınların sosyo-ekonomik olarak güçlendirilmesi (örneğin, eğitime ve mikro kredi planlarına erişimin iyileştirilmesi);
- Yaşlı nüfus için sosyal destek (örneğin arkadaşlık girişimleri, yaşlılar için toplum ve gündüz merkezleri);
- Azınlıklar, yerli halk, göçmenler ve çatışmalardan ve afetlerden etkilenen insanlar da dahil olmak üzere savunmasız insanları hedef alan programlar (örneğin, afetlerden sonra psiko-sosyal müdahaleler);
- Okullarda ruh sağlığını geliştirme faaliyetleri (örneğin, okullarda destekleyici ekolojik değişiklikleri içeren programlar);
- İşyerinde ruh sağlığı müdahaleleri (örneğin, stres önleme programları);
- Konut politikaları (örneğin, konut iyileştirme);
- Şiddet önleme programları (örneğin, alkol ve silahlara erişimin azaltılması);
- Toplumsal kalkınma programları (örneğin, entegre kırsal kalkınma);
- Yoksullar için yoksulluğun azaltılması ve sosyal koruma;
- Ayrımcılıkla mücadele yasaları ve kampanyaları;
- Ruhsal bozukluğu olan bireylerin haklarının, fırsatlarının ve bakımının teşviki.

Ruh sağlığı bilgi stratejisi; bağlam, ihtiyaçlar, girdiler, süreçler ve sonuçları içermelidir. Bilgi sistemleri klinisyenler, yöneticiler, planlayıcılar ve politika yapıcılar için temel bir kaynak sağlar ve denetim döngüsünün ilerlemesine olanak tanır (Jenkins, 2008).

Ülkelerin, politikanın uygulanmasını ve hizmetlerin sunulmasını yürütmek için sürdürülebilir bir insan kaynakları stratejisine ihtiyacı vardır. Düşük gelirli ülkeler, sağlık ve sosyal bakım profesyonelleri için tüm eğitim gereksinimlerini karşılamakta zorluk yaşamaktadırlar. Bu nedenle hem evde hem de başka yerlerde birinci ve ikinci basamak sağlık personelinin yetişmesi ve bu personellerin eğitimi için sürdürülebilir bir plana ihtiyaçları olacaktır (Gureje ve Jenkins, 2007).

Kullanıcı katılımı, ruh sağlığındaki en büyük yeniliklerden biridir ve ruh sağlığı hizmetlerini kullanan insanları, onları etkileyen kararların ve faaliyetlerin merkezine yerleştirmek için bir çerçeve sağlar. Ruhsal hastalığı olan kişiler ve bu kişilerin aileleri, sağlık ve bakım personeli ve toplum; ruh sağlığı hizmetlerinin bileşenleridir. Eksiklikleri ve sorunları tespit edebildikleri ve neyin iyi çalıştığı hakkında yorum yapabildikleri için onların katılımı, hizmetlerin planlanmasını ve sunumunu büyük ölçüde iyileştirebilir (Mirza vd., 2006).

Tüm ülkeler, politika geliştirme ve uygulama programını desteklemek için sürdürülebilir bir araştırma ve geliştirme stratejisi oluşturmalıdır. Epidemiyoloji ve ruh sağlığı, politika ve planlamaya önemli katkılarda bulunur. Politika yapıcıların hem niteliksel hem de niceliksel bilgilere ihtiyacı vardır. Ayrıca sosyal politikalar, mümkün olan her yerde kanıta dayalı olma ilkesine tabi olmalıdır (Jenkins, 2008).

Her ülkenin, bireylerin haklarının yasal olarak korunması ihtiyacına ve kasıtsız gözaltı ve tedavinin gerçekleşebileceği durumların düzenlenmesine rıza gösterilmediği zaman, profesyonellerin insanları tedavi etme ihtiyaç ve isteklerini dengeleyen bir yasal çerçeveye ihtiyacı vardır. Ülkeler ayrıca engellilik, ayrımcılıkla mücadele ve sosyal yardımlar hakkında mevzuat geliştirmelidir (Mathers ve Loncar, 2006).

Ruh sağlığı politikasını geliştirirken, ruh sağlığı sorunları ve ruhsal hastalık hakkında damgalanmanın dikkate alınması önemlidir. Damgalanma sadece ruhsal hastalığı olan birey üzerinde etkili olmaz; ruh sağlığı hizmeti sunan kurumları ve çalışanları, aynı zamanda sistemi etkiler. Ruhsal hastalığı olan kişilerin sosyal olarak dışlanmasına neden olan damgalama, yalnızca ruhsal hastalığı olan kişiler için değil, aynı zamanda bir bütün olarak toplum sağlığı için de zararlıdır (Jenkins, 2008).

Dünyada ve Türkiye'de Ruh Sağlığı Politikaları

Dünyada Ruh Sağlığı Politikaları

Dünyada ruh sağlığı hizmetlerinin sunumu noktasında dünyada üç farklı hizmet modeli bulunmaktadır. Bunlar 1800'lü yıllardan 1960'lı yıllara kadar yaygın kullanılan "Hastane Temelli Model", 1960'lı yıllardan sonra gelişmiş ülkelerde yaygın kullanılmaya başlanan "Toplum Temelli Model" ve son

olarak karma bir model olan "Toplum-Hastane Denge Modeli" olarak karşımıza çıkmaktadır (Thornicroft ve Tansella, 2002).

Dünya genelinde ruhsal hastalıkların yükü ile ruh sağlığına ayrılan kaynaklar arasında büyük bir orantısızlık vardır. Dünyada sağlık hizmetlerine ayrılan toplam bütçenin %2,82'si ruh sağlığına ayrılmaktadır. Yüksek gelir grubundaki ülkelerin toplam sağlık harcamaları içinden ruh sağlığına ayırdığı pay %5,1 iken, düşük gelirli ülkelerde %0,53'tür. Düşük ve orta gelir grubunda bulunan ülkelerde ruh sağlığına ayrılan bütçenin büyük bir bölümü akıl hastanelerine harcanmaktadır. Ruh sağlığı alanında çalışan personel sayısında da ülkelerin gelir grubuna göre büyük farklılıklar vardır. Ülkelerin gelir düzeyi arttıkça, ruh sağlığı alanında çalışan personel sayısının arttığı görülmektedir. Dünyada 100.000 kişiye düşen toplam ruh sağlığı çalışanı sayısı 10,3'tür. Yüksek gelir grubundaki ülkelerde 100.000 kişiye düşen ruh sağlığı çalışanı sayısı 50,8 iken düşük gelirli ülkelerde bu sayı 1,3'tür (Songur vd., 2017).

Ruh sağlığına ayrılan kaynakların akıl hastanelerine yönlendirildiği ülkelerde, hastanelere ulaşım zorluğu ve yatak sayısının yetersizliği gibi nedenlerden dolayı hastalar ihtiyacı olan hizmetleri alamamaktadırlar. Ruh sağlığı hastalarının çok çeşitli ihtiyaçları vardır ve akıl hastanelerinin tek başına tüm bu ihtiyaçları karşılaması beklenemez. Buna rağmen dünyadaki ülkelerin %80'inde akıl hastanesi vardır ve genellikle kaynakların büyük bir kısmı bu hastanelere ayrılmaktadır. Akıl hastaneleri sadece şizofreni gibi ağır ruh sağlığı hastalarına hizmet vermek için oluşturulmuş yapılardır. Hastanelerde verilen EKG ve ilaç tedavisi hastalığın sadece alevlenme dönemine yöneliktir (Songur vd., 2017).

Avrupa ülkelerinin birçoğu, hastane temelli modeli terk ederek toplum temelli modele geçiş sürecini tamamlamıştır. Ülkelerin hemen hepsinde ruh sağlığı hastalarına yaşadığı çevrede hizmet sunacak kurumlar oluşturulmuştur. Toplum temelli ruh sağlığı modeli 1961 yılında İtalya'daki ruh sağlığı reformu ile başlamış, son 30 yılda Avrupa ülkelerinin hemen hepsinde bu uygulamaya geçilmiştir. İtalya'da başlayan değişim eş zamanlı olarak Finlandiya, Almanya, İngiltere ve Fransa gibi ülkelerde de tamamlanmıştır (Yanık, 2007).

Ruh sağlığı sorunları dünyada artmaktadır. Temel olarak demografik değişiklikler nedeniyle son on yılda ruh sağlığı sorunlarında ve madde kullanım bozukluklarında %13'lük bir artış olmuştur. Dünyadaki çocuk ve ergenlerin yaklaşık %20'sinin ruh sağlığı sorunu var ve intihar, 15-29 yaşındakiler arasında ikinci önde gelen ölüm nedenidir. Çatışma sonrası ortamlarda yaklaşık her beş kişiden birinin ruhsal sağlık sorunu vardır. Ruh sağlığı sorunları; okul veya iş performansı, aile ve arkadaşlarla ilişkiler ve topluluğa katılma yeteneği gibi yaşamın tüm alanları üzerinde önemli bir etkiye sahip olabilir. En yaygın ruh sağlığı sorunlarından ikisi olan depresyon ve anksiyete, küresel ekonomiye her yıl 1 trilyon ABD dolarına mal oluyor. Bu rakamlara rağmen, ruh sağlığına giden devlet sağlık harcamalarının küresel medyanı %2'den azdır (World Health Organization, 2021).

Dünya Sağlık Örgütü, 2013 yılında Kapsamlı Ruh Sağlığı Eylem Planı"nı onaylamıştır. Plan, tüm üye devletlerin ruh sağlığını iyileştirmek ve bir dizi küresel hedefe ulaşılmasına katkıda bulunmak için belirli eylemlerde bulunma taahhüdüdür. Eylem Planı'nın genel amacı; ruhsal sağlığı geliştirmek, ruhsal bozuklukları önlemek, bakım sağlamak, iyileşmeyi hızlandırmak, insan haklarını geliştirmek ve ruhsal bozukluğu olan kişiler için ölüm, hastalık ve sakatlık oranlarını azaltmaktır. Eylem Planı'nda insan haklarının korunması ve geliştirilmesine, sivil toplumun güçlendirilmesine ve toplum temelli bakımın merkezi konumuna özellikle vurgu yapılmaktadır. Plan, dört temel hedefe odaklanır (World Health Organization, 2021):

1. Ruh sağlığı için etkili liderliği ve yönetimi güçlendirmek,
2. Toplum temelli ortamlarda kapsamlı, entegre ve duyarlı ruh sağlığı ve sosyal bakım hizmetleri sağlamak,
3. Ruh sağlığının teşviki ve hastalıkların önlenmesi için stratejiler uygulamak ve
4. Ruh sağlığı için bilgi sistemlerini, kanıtları ve araştırmaları güçlendirmek.

Dünyada ruh sağlığı politikalarına yönelik uygulamalar, bazı ülkeler üzerinden aşağıda örneklendirilmiştir.

İngiltere'de Ruh Sağlığı Politikaları

İngiltere, geçmiş siyasi ve ekonomik göstergeleri açısından olduğu kadar sağlık politikaları ve uygulamaları açısından da dünyada önemli bir yere sahiptir. Beveridge ve Ulusal Sağlık Sistemi ile sembolize edilen İngiltere sağlık politikası, diğer ülkelerde olduğu gibi kronolojik olarak değişim göstermiştir. İngiltere'deki ruh sağlığı politikaları literatür (Eke ve Kişi, 2019; Glasby vd., 2021; Brown vd., 2023; Garratt, 2023; Jones, 2023) bilgileri doğrultusunda aşağı özetlenmiştir.

Birleşik Krallık'taki ruh sağlığı politikaları, yıllar içinde ruh sağlığı sorunlarıyla mücadele eden bireylerin ihtiyaçlarını karşılayacak şekilde gelişmiştir. Bu politikalar ruh sağlığı hizmetlerine erişim sağlamayı, damgalamayı azaltmayı ve genel ruhsal refahı geliştirmeyi amaçlamaktadır. Ocak 2022'de ruh sağlığı politikalarında güncellemelere gidilmiştir. Ulusal Sağlık Hizmeti

(NHS), Birleşik Krallık'ta ruh sağlığı hizmetlerinin birincil sağlayıcısıdır.

Ciddi ruhsal sağlık sorunları olan kişiler için kriz müdahalesi, ayakta tedavi ve yatarak tedavi dâhil olmak üzere bir dizi hizmet sunmaktadır. "Ruh Sağlığında Beş Yıllık İleriye Bakış" gibi girişimler yoluyla ruh sağlığı hizmetlerine erişimin iyileştirilmesine yönelik bir taahhüt bulunmaktadır. 2007'de revize edilen 1983 tarihli Ruh Sağlığı Yasası, kendilerinin veya başkalarının güvenliği için gerekli olması halinde ciddi ruhsal bozukluğu olan bireylerin gözaltına alınmasına yönelik yasal bir çerçeve sunmaktadır. Yasa aynı zamanda gözaltı kriterlerini, gözaltına alınan kişilerin haklarını ve sağlık çalışanlarının, aile üyelerinin ve sürece dâhil olan diğer kişilerin rollerini belirlemektedir (Eke ve Kişi, 2019; Brown vd., 2023).

2016'da yayınlanan Ruh Sağlığında Beş Yıllık İleriye Bakış, Birleşik Krallık'ta ruh sağlığı hizmetlerini iyileştirmeye yönelik bir planın ana hatlarını çizmektedir. Ruh sağlığı hizmetlerine yatırımın artırılması, tedaviye erişimin genişletilmesi ve bekleme sürelerinin kısaltılması gibi hedefleri içermektedir. Plan, ruh sağlığı hizmetlerinin birinci basamak ve diğer sağlık hizmetleriyle entegrasyonunu vurgulamaktadır. Birleşik Krallık hükümeti, ruh sağlığı hizmetlerine zamanında erişimi sağlamak için erişim ve bekleme süresi standartlarını uygulamaya koymuştur. Örneğin, psikoterapi hizmetlerine erişim ve psikoz hizmetlerinde erken müdahale için maksimum bekleme süreleri konusunda standartlar bulunmaktadır (Glasby vd., 2021; Garratt, 2023).

Ruh sağlığı sorunlarıyla ilgili damgalamayı azaltmak, ruh sağlığı politikalarının çok önemli bir parçasıdır. Çeşitli damgalama karşıtı kampanya ve programlar, farkındalığı artırmayı ve halkın ruh sağlığına ilişkin algılarını değiştirmeyi amaçlamaktadır. Erken müdahalenin önemi kabul edilen çocuklara ve gençlere yönelik ruh sağlığı hizmetlerinin iyileştirilmesine odaklanılmaktadır. "Geleceğin Ruhunda" raporu gibi girişimler bu çalışmalar için bir çerçeve sağlamaktadır. Bireylerin evlerine daha yakın bir yerde desteğe erişmelerine olanak tanıyacak şekilde topluluklar içinde ruh sağlığı hizmetleri sağlanmasına önem verilmektedir. Buna Kriz Çözümü ve Evde Tedavi Ekipleri gibi girişimler de dâhildir. İngiltere, ruh sağlığı politikalarının değişebileceğini ve gelişebileceğini Ocak 2022'deki son güncellemeler sonrası göstermiştir (Brown vd., 2023; Garratt, 2023; Jones, 2023).

Almanya'da Ruh Sağlığı Politikaları

Almanya'da ruh sağlığı politikaları sağlık sisteminin bir parçası olarak, genellikle federal, eyalet ve yerel düzey olmak üzere çeşitli düzeylerde kamu ve özel sağlık hizmeti sağlayıcıları tarafından sunulmaktadır. Almanya, ruh sağlığı sorunlarını ele almak için kapsamlı bir sisteme sahiptir. Herkesin zorunlu bir sağlık sigortası olması gerekir ve bu sigorta, temel sağlık hizmetlerini kapsar ve ruh sağlığı hizmetlerini de içerir. Ruh sağlığı hizmetleri; hastanede yatarak tedavi, ayakta tedavi, psikoterapi gibi çeşitli şekillerde sunulabilir (Schilling vd., 2021; Porst vd., 2022).

Ruh sağlığı hizmetleri; psikiyatristler, psikologlar, psikoterapistler ve diğer uzmanlar tarafından sunulmaktadır. Bu profesyoneller genellikle özel pratisyenler olarak çalışabilir veya kamu sağlık kuruluşları ve özel hastanelerde istihdam edilebilirler. Psikoterapi, ruh sağlığı hizmetlerinin önemli bir parçasıdır. Psikoterapi, bireylerin duygusal ve zihinsel problemleriyle başa çıkmalarına yardımcı olmak için kullanılan bir tedavi yöntemidir ve bu hizmet, lisanslı psikoterapistler tarafından sunulmaktadır. Bireyler, hekimleri aracılığıyla yardım isteyebilir ve pratisyen hekimleri de gerektiğinde onları uzmanlara yönlendirebilir. Almanya iyi gelişmiş bir psikoterapi sistemine sahiptir. Psikoterapistler kapsamlı bir eğitimden geçmekte ve çeşitli psikoterapi biçimleri sunmak için lisans almaktadırlar. Ayrıca psikoterapistlere sağlık sigortası sistemi üzerinden ödeme yapılmasına yönelik hükümler de bulunmaktadır (Peitz vd., 2021; Mauz vd., 2023; Thom vd., 2023).

Ruh sağlığı hizmetlerine erişim genellikle iyi düzenlenmiştir. Ancak, uzun bekleme süreleri veya belirli bölgelerde hizmet eksikliği gibi sorunlar olabilmektedir. Ruh sağlığını teşvik etmeye ve ruh sağlığı sorunlarını önlemeye yönelik girişimler bulunmaktadır. Bu girişimler arasında eğitim programları, farkındalık kampanyaları ve toplum temelli müdahaleler yer almaktadır. Ruh sağlığı konularında kamu bilincini artırmaya yönelik kampanyalar ve eğitim programları, toplumun ruh sağlığı konularına duyarlılığını artırmayı amaçlamaktadır (Gühne ve Heller, 2019; Schilling vd., 2021).

Ruh sağlığı, birinci basamak sağlık sistemine entegre edilmiştir. Pratisyen hekimler genellikle ruh sağlığı sorunları için yardım arayan bireylerin ilk temas noktasıdır. İlk değerlendirmeleri yapabilir ve gerekirse hastaları uzmanlara yönlendirebilirler. Almanya, hem yatarak hem de ayakta tedavi dâhil olmak üzere bir dizi ruh sağlığı hizmeti sunmaktadır. Yatarak tedavi psikiyatri hastanelerinde veya genel hastanelerdeki özel birimlerde sağlanırken, ayakta tedaviye özel muayenehaneler ve klinikler aracılığıyla erişilebilir. Ruhsal krizler ve acil durumlar için acil servisler ve kriz müdahale merkezleri bulunmaktadır. Akut ruh sağlığı krizleri yaşayan bireyler için krize müdahale hizmetleri mevcuttur. Bu hizmetler arasında yardım hatları, mobil kriz ekipleri ve kriz stabilizasyon birimleri yer almaktadır (Peitz vd., 2021; Porst vd., 2022; Thom vd., 2023).

Almanya'da ruh sağlığı sorunları olan bireylerin haklarını korumak

için yürürlükte olan yasa ve yönetmelikler bulunmaktadır. Das Psychisch-Kranken-Hilfe-Gesetz (PsychKHG), ruhsal hastalığı olan bireylerin hak ve sorumluluklarını özetleyen bu tür bir yasadır. Almanya ruh sağlığı alanında güçlü bir araştırma geleneğine sahiptir. Ruh sağlığı sorunlarını anlamak, tedavi etmek ve bakım için yenilikçi yaklaşımlar geliştirmeye yönelik araştırmalar, çalışmalar, projeler ve çabalar devam etmektedir. Ayrıca ruhsal sağlık sorunlarıyla mücadele eden bireylere yönelik toplumda olumsuz tutumların azaltılması ve stigmanın kırılması için çeşitli programlar yürütülmektedir. Anlayış ve kabulü artırmak için farkındalık kampanyaları ve eğitim programları uygulanmaktadır (Gühne ve Heller, 2019; Schilling vd., 2021; Mauz vd., 2023).

İtalya'da Ruh Sağlığı Politikaları

İtalya'daki ruh sağlığı politikaları, ruh sağlığı sorunları olan bireylerin refahını ve tedavisini teşvik etmek üzere tasarlanmıştır. İtalya, diğer birçok ülke gibi ruh sağlığı sorunlarının ele alınmasının önemini kabul etmiş ve ihtiyacı olanlara daha iyi bakım ve destek sağlamak için politikalar ve girişimler uygulamaya koymuştur. Ruh sağlığı politikaları, ruh sağlığı hizmetlerinin düzenlenmesini, finansmanının sağlanmasını ve destekleyici stratejilerini içermektedir. İtalya, ruh sağlığı hizmetlerini iyileştirmeye yönelik stratejileri ve hedefleri belirleyen Ulusal Ruh Sağlığı Planına (Piano Nazionale della Salute Mentale) sahiptir. Plan, toplum temelli bakım, önleme ve ruh sağlığı sorunları yaşayanların damgalanmasının azaltılmasına odaklanmaktadır (Girolamo vd., 2020; Sani vd., 2020; Scendoni vd., 2022; Carbone, 2023).

Ruh sağlığı sorunlarının erken teşhisi ve müdahalesi, uzun vadeli olumlu sonuçlar sağlamış ve bu nedenle erken tanı ve müdahale programları teşvik edilmektedir. Ruh sağlığına yönelik toplumunun bilincini ve farkındalığı artırmak ve ruh sağlığı sorunlarını çevreleyen damgalamayı azaltmak için ruh sağlığını geliştirme ve eğitim girişimleri desteklenmektedir. Okullar ve topluluklar, halkın ruh sağlığı ve refahı konusunda eğitilmesini sağlamak için genellikle programlara dâhil olmaktadır (Mancini ve Prati, 2022; Ussai vd., 2022; Amerio vd., 2023).

Ruh sağlığı hizmetlerine erişim, herkes için kolay ve adil olmalıdır. Bu nedenle hizmet kapasitesinin arttırılması, hizmet sunumunda kalitenin sağlanması ve hizmetlerin yaygınlaştırılması önemlidir. Ruh sağlığı sorunları, sadece psikiyatrik tedavi ile değil, aynı zamanda psikososyal destek, terapi, sosyal hizmet ve diğer disiplinlerin entegre edildiği bir tedaviyle ele alınmalıdır. Bu nedenle İtalya, büyük psikiyatri hastanelerini kapatarak ve toplum temelli bakıma geçerek ruh sağlığı hizmetlerini kurumsuzlaştırmak için önemli çabalar sarf etmiştir. Bu yaklaşımla, ruh sağlığı sorunları olan bireyleri büyük kurumlarda izole etmek yerine bu bireylere kendi toplulukları içinde bakım ve destek sağlamayı amaçlamaktadır (Rossi vd., 2020; Scendoni vd., 2022; Ferrara vd., 2023).

İtalya, ruh sağlığı sorunları olan bireylerin haklarını korumak için yürürlükte olan bir ruh sağlığı mevzuatına sahiptir. 1978 tarih ve 180 sayılı Basaglia Yasası, kurumsuzlaştırma ve toplum temelli bakımı teşvik ederek ruh sağlığı politikalarının şekillendirilmesinde önemli bir rol oynamıştır. Bu yasa ayrıca, insan haklarının önemini ve ruh sağlığı sorunları olan bireylerin onurunu vurgulamaktadır. Bu doğrultuda kolay erişilebilir ve toplum temelli ruh sağlığı hizmetleri sağlamak için Toplum Ruh Sağlığı Merkezleri ağı kurmuştur. Bu merkezlerde değerlendirme, danışmanlık, terapi ve sosyal destek de dahil olmak üzere bir dizi hizmet sunulmaktadır (Sani vd., 2020; Carbone, 2023).

İtalya, ruh sağlığı krizlerinde bireylere anında destek sağlamak için yardım hatları ve mobil kriz birimleri de dâhil olmak üzere krize müdahale hizmetlerini uygulamaya koymuştur. Bu hizmetler acil servis ziyaretlerini ve hastaneye yatışları önlemeye yardımcı olmaktadır. Ayrıca ruh sağlığı sorunları olan bireylerin rehabilitasyonunu ve işgücüne yeniden entegrasyonunu desteklemek için çaba gösterilmektedir. İş eğitimi ve istihdam fırsatlarına odaklanan programlar bu çabaların bir parçasıdır (Girolamo vd., 2020; Ussai vd., 2022; Amerio vd., 2023).

Ruh sağlığı alanındaki bilimsel araştırmaların desteklenmesi ve politikaların devam ettirilmesi; ruh sağlığı politikaları oluşturulurken insan haklarına saygı gösterilmesi ve kültürel etkilere duyarlı olması; bireylere bütünlük içinde bir sağlık hizmeti sunabilmek için ruh sağlığı hizmetlerinin genel sağlık hizmetlerine entegre edilmesi; politika kararlarının etkilerini görebilmek ve ruh sağlığı hizmetlerinin kalitesini artırmak için ruh sağlığı konusunda araştırmaların yürütülmesi ve veri toplanması önemlidir (Rossi vd., 2020; Moro vd., 2022; Scendoni vd., 2022).

Sağlık sisteminin merkezi olmayan yapısı nedeniyle ruh sağlığı politikalarının ve hizmetlerinin İtalya'da bir bölgeden diğerine farklılık gösterebileceğini belirtmek önemlidir. Toplum temelli bakımın ve damgalanmanın azaltılmasının teşvik edilmesinde önemli ilerlemeler kaydedilmiş olsa da daha fazla finansman ihtiyacı, daha fazla damgalama çabası ve ruh sağlığı hizmetlerine ihtiyaç duyan tüm bireyler için bakıma erişimin iyileştirilmesi gibi zorluklar devam etmektedir (Sani vd., 2020; Mancini ve Prati, 2022; Amerio vd., 2023).

Türkiye'de Ruh Sağlığı Politikaları

Türkiye'de ruh sağlığı hizmetleri temel olarak hastaneler ve

topluluk temelli kurumlarda (Toplum Ruh Sağlığı Merkezleri) verilmekte ve hizmetler genelde çok kalabalık ve aşırı yüklü olup, ağırlıklı ilaç kullanımına dayalı katı bir tıbbi yönelimle çalışmaktadır. Ruh sağlığı yasal düzenlemeleri güncel değildir ve ruh sağlığı problemi yaşayan kişiler, aileleri ve hizmet veren uzmanlar için de insan hakları farkındalığı çok düşüktür. İstemsiz yatış/yerleştirme ve zorla tedavi önemli meselelerden biridir; ancak bu konuda yeterli resmi veri bulunmamaktadır. Türkiye halen yasal ehliyetten tamamen mahrum bırakma uygulamasını yapmakta ve vasilik düzenlemesi yürürlüktedir. Türkiye'de ruhsal sorun yaşayan yetişkinlerin çoğunluğu aileleriyle birlikte yaşamaktadır. Topluluk temelli yatılı destekler çok sınırlıdır. Türkiye'deki topluluk temelli ruh sağlığı desteği temel olarak ayaktan tedavi verilen toplum ruh sağlığı merkezlerini (TRSM) kapsamaktadır. Bu merkezler hastanelerle ilişkili statülerine göre tanımlanmaktadır (Turnpenny vd., 2018).

Dünya Sağlık Örgütü'nün, Ruh Sağlığı Gereksinimi Eylem Programı Türkiye'de, 2017 itibariyle, Sağlık Bakanlığı ve DSÖ iş birliğiyle birinci basamak sağlık uzmanları için başlatılmıştır. Psikiyatrist, psikolog, psikolojik danışman ve sosyal çalışmacılardan oluşan bir grup eğitimci birinci basamak uzmanlarına eğitimler vermektedir. Türkiye'de akran destek grupları, daha çok madde ve alkol bağımlısı kişiler için bulunmaktadır. Bazı şizofreni dernekleri kendilerinin de akran desteği sunduğunu savunmaktadır. Bu derneklerin büyük çoğunluğu aile üyelerince yürütülmektedir. Bazen de gönüllü psikiyatristler, hemşireler, psikologlar psikoeğitim grupları yapmaktadır. Bu dernekler, ayrıca kültürel ve beceri eğitimi fırsatları da sunmaktadır. TRSM'ler ve psikiyatri hastaneleri de bu tür kültürel ve mesleki beceri eğitimleri sağlamaktadır (World Health Organization, 2021).

Engellilikle ilgili ödemeler olmasına rağmen (örneğin engelli maaşı, bakıcı ödemesi gibi) kişisel asistanlık ve kişisel bütçe sistemi Türkiye'de uygulanmamaktadır. Aile üyeleri sadece "ağır engelli" kişilerin bakım vereni olarak ve engelli kişinin vasisi olmaları durumunda ödeme alabilmektedir. Bu alanda çalışan bazı hizmet elemanları ve bazı STK üyeleri vasilerin engelli bakım parasını nadiren hastaların iyilik halini artırmak için kullandığını genelde kendilerinin gündelik yaşam ihtiyaçlarına harcadığını dile getirmektedir. Türkiye, BM EKHS'ni 2008'de ve ek protokolü de 2014'te onaylamış olsa da zorunlu yatış/yerleştirme ve tedaviyi düzenleyen bazı yasal düzenlemelere karşın bir ruh sağlığı yasasına sahip değildir. Tecrit, uzun süreli fiziksel tespit (kısıtlama) ve kimyasal tespit istatistiki bilgiler olmasa da oldukça yaygın uygulanmaktadır (Turnpenny vd., 2018).

Sosyal Politika

Sosyal politika bir çalışma alanı olarak insan ihtiyacına ve devletlerin bunu karşılamak için neler yapabileceğine odaklanır. İkinci Dünya Savaşı'ndan sonra, refah devletinin yükselişiyle birlikte batı ülkelerinde akademik bir uygulama alanı olarak gelişmiştir (Taylor, 2019).

19. yüzyılda yaşanan ekonomik ve sosyal gelişmeler sonucunda ortaya çıktığı düşünülen sosyal politika, sanayi devrimi ile anlam kazanmaya başlamıştır. Sanayi devrimi ile birlikte ekonomik ilişkilerin değişmesi sonucunda toplumsal değişimler kaçınılmaz hale gelmiştir. Sanayi devrimi ile artan üretim, daha fazla emek ihtiyacını doğurmuş, sermaye sahiplerinin emek piyasasındaki hâkimiyeti, ticaretin serbestleşmesiyle daha da artmıştır (Aravacik, 2018).

Liberal piyasa ekonomisi yaklaşımının benimsendiği bu dönemde, devlet müdahalelerinin serbest piyasayı olumsuz etkileyeceği görüşü hâkim olmuştur. Müdahalesiz oluşan bir piyasanın halkı zenginleştireceği inancı, bir yandan sermaye sahiplerinin zenginleşmesini sağlarken, diğer yandan emek sektörünün fakirleşmesine neden olmuştur. Çocukların ve kadınların karşılaştığı yoksulluk, insani duyguları incitmiştir. İşçi ücretlerine ve çalışma koşullarına herhangi bir müdahalenin yapılmadığı bu dönemde artan yoksulluk, toplumsal sorunların artmasına ve dolayısıyla sosyal politikaların hızla gelişmesine neden olmuştur (Robinson ve Moggridge, 2013). Ekonomide liberal yaklaşımın bir sonucu olarak toplumda iki karşıt kesim ortaya çıkmıştır: Sermaye sahipleri olan burjuva sınıfı ve emek sahipleri olan işçi sınıfı. Ücretlerin düşmesi, olumsuz çalışma koşulları ve uzun çalışma saatleri işçi sınıfında toplumsal sorunlara ve sınıf çatışmalarına yol açmıştır. 19. yüzyılda devletin liberal ekonomi anlayışının yol açtığı toplumsal sorunları çözmek için sosyal politikalar uygulanmıştır. Devletin çalışma hayatına, çalışma ilişkilerine ve ücretlere müdahalesi ile toplumsal barış ve adaletin sağlanması kaçınılmaz olmuştur (Erdut, 2002).

1880-1920 yılları arasında İngiltere ve Kanada'da başlayan sosyal reform hareketleri ile sosyal politikalar yasaklayıcı yaklaşımdan tanımlayıcı bir yaklaşıma dönüşmüştür. Bu yaklaşımda, çalışma hayatındaki rolünün sınırlı ve katı olduğu konusunda devlet eleştirilmiş ve çalışma hayatındaki olumsuzlukların giderilmesi için devletin sosyal koşulları düzenlemesi gerektiği önerilmiştir. Bu dönemde Fransa, Almanya, ABD gibi kapitalist gelişmiş ülkelerde devletin sosyal politikalardaki rolünün artması gerektiği görüşü hakim olmuştur (Ersöz, 2011).

Sonuç olarak modern anlamda sosyal politikanın ortaya çıkışı, entelektüel-politik alanda Fransız Devrimi'nin, sosyal

ve ekonomik alanda ise sanayi devriminin meydana getirdiği sosyal koşullara atfedilir. İkinci Dünya Savaşı sonrasında gelişmiş ülkelerde liberal ekonomik yaklaşımlar terk edilmiş, devletin sosyal politikalara müdahale etmesi gerektiği inancıyla Keynesyen politika yaklaşımı benimsenmiştir. Bu yaklaşımın benimsenmesinde bir diğer önemli faktör ise 1929 ekonomik krizi ve bunun olumsuz sonuçlarıdır. Sanayi devriminden sonra sosyal politikaların kapsamı genişlemiş, sadece emek sektörünün değil tüm toplumun sorunlarına değinilmiştir. Sağlık hizmetleri, yaşlı ve çocuk bakımı, işsizlik ve yoksullukla mücadele, kadınların çalışma yaşamına katılımı, çevrenin korunması, cinsiyet ayrımcılığı gibi konuların tamamı devletin sosyal politika kapsamında mücadele ettiği konular haline gelmiştir (Çubuk, 1979).

'Sosyal politika', politika kavramının yalnızca bir yönünü temsil etmektedir. Bir devletin birçok politikası olabilir. Örneğin, dış politika, finans ve ticaret politikası, askeri veya savunma politikası, gelir politikası, eğitim politikası, gençlik politikası, nüfus politikası, işgücü politikası gibi farklı alanlarda farklı şekillerde çalışan birçok politika türünü sıralayabiliriz. Toplumsal sorunlara yönelik olan konular, sosyal politikanın sınırları içerisine girmektedir. Sosyal politikanın alanı çok geniştir. Aslında, büyük ölçüde bir toplumu tanımlamaya hizmet eder. Bir topluluğun en zayıf üyelerini korumayı amaçlarken; aynı zamanda herkesin sosyal ihtiyaçlarını da karşılaması gerekir. Sosyal politikanın kökenleri; sosyoloji, demografi, siyaset bilimi, sosyal felsefe, psikoloji, ekonomi ve tarihe dayanır (Taylor, 2019; Haque, 2021).

Sosyal politika, sosyal hayatın ihtiyaçlarına yönelik çözümler üretme anlamına gelen kapsayıcı bir disiplindir. Sosyal sorunlar, ekonomik ve çevresel faktörlere bağlı olarak değişmekte ve bu değişimler toplumsal yapıya ve devlet politikalarına göre de farklılık göstermektedir (Aravacik, 2018).

Sosyal politika, topluma veya toplumun belirli bir kesimine fayda sağlayacak değişiklikleri uygulamaya yönelik hükümet ve yasama çabalarını ifade eder ve bu anlamda bir sosyal müdahaledir (Kazdin, 2001).

Ruh Sağlığı ve Sosyal Politika İlişkisi

Ruh sağlığı, bireylerin zihinsel, duygusal ve sosyal iyi olma halini ifade eder. Ruh sağlığı politikaları ise toplumun ruh sağlığını koruma ve iyileştirme amacıyla geliştirilen stratejiler, yasalar ve uygulamalardır. Sosyal politika, toplumun genel refahını artırmayı hedefleyen, özellikle sağlık, eğitim, sosyal güvenlik ve istihdam gibi alanlarda yapılan düzenlemeler ve uygulamalardır. Ruh sağlığı ve sosyal politikalar, bireylerin ve toplulukların genel refahını artırmak için önemli iki alandır.

Ruhsal hastalıklar, dünya çapında engelliliğin önde gelen nedenidir (Vigo vd., 2016). Ruh sağlığı politikasının genel sağlık politikasıyla ilişkilendirilmesi ve herhangi bir genel halk sağlığı konusunda fiziksel sağlığın yanı sıra ruhsal sağlığın da ele alınması özellikle önemlidir. Epidemiyolojik çalışmalar, genel popülasyonda yaygın ruhsal bozuklukların prevalansının yüksek olduğunu ve ayrıca bunların şiddetli, sakatlayıcı ve uzun süreli olabildiğini göstermektedir (Jenkins, 2008).

OECD, çalışma çağındaki her beş kişiden birinin herhangi bir zamanda bir ruh sağlığı sorunu yaşadığını ve her iki kişiden birinin de yaşamı boyunca bir akıl hastalığı yaşayacağını tahmin etmektedir (Simpson vd., 2021). Buna ek olarak, düşük sosyo-ekonomik statüye sahip kişilerin ekonomik yönden daha savunmasız olması nedeniyle ruh sağlığı sorunları geliştirme ve deneyimleme konusunda risk oranları daha yüksektir. Örneğin; işsiz veya ekonomik olarak aktif olmayan bireylerin, çalışan bireylere göre daha kötü ruh sağlığı sonuçlarına sahip olma durumları olabilir (Flatau vd., 2000). Benzer şekilde, yoksulluk içinde olanların veya maddi sıkıntı yaşayanların da yüksek gelir gruplarındaki insanlara göre orantısız bir ruhsal hastalık yükü yaşama durumu vardır (Silva vd., 2016).

Yoksulluk ve ruh sağlığı iç içedir ve ilişki nedenselliği her iki yönde de yansıtır: Yoksulluk akıl sağlığını kötüleştirir ve akıl hastalığı yoksul insanları daha da yoksullaştırır. Bu nedenle, ruh sağlığı hizmetlerinin etkin bir şekilde sağlanması, genel sağlık stratejilerinin yanı sıra ulusal yoksulluğun azaltılmasının ayrılmaz bir parçasını oluşturmalıdır (Gureje ve Jenkins, 2007). Ruhsal bozukluklar dünyanın her yerinde yaygındır ve sakatlık, ölüm oranı, ekonomik üretkenlik kaybı ve yoksulluğa neden olur. Savaşlar, artan mülteci sayısı, HIV/AIDS'in etkisi ve beslenme yetersizlikleri, yoksul ülkelerde yaşayanların ruh sağlığı sorunlarının yükünü daha da artırmaktadır (Mathers ve Loncar, 2006).

Diğer taraftan ebeveynlerin hastalığı, çocukların yani gelecek nesillerin entelektüel ve duygusal gelişimlerine olumsuz etkide bulunur. Ayrıca tedavi edilmemiş ruhsal bozuklukların varlığı, fiziksel hastalıklara yönelik önleme ve tedavi programlarının başarısını da etkiler (Jenkins, 2008). Ruh sağlığı politikalarının benimsenmesi ve ruh sağlığı politikasının halk sağlığı politikasına ve genel sosyal politikaya entegre edilmesi önemlidir, çünkü ruh hastalığı diğer sağlık ve kalkınma hedeflerinin gelişmesini engeller, neden olur, fiziksel sağlığı etkiler ve sonuçta toplumlar için ağır bir yüke neden olur (Gureje ve Jenkins, 2007).

Kültürel konular da çok önemlidir. Toplumun ruh sağlığına verdiği değeri, semptomların ortaya çıkışını, hastalık davranışını,

hizmetlere erişimi, bakıma giden yolları, bireylerin ve ailelerin hastalığı yönetme biçimini, toplumun hastalığa tepki verme şeklini, kabullenme derecesini, hastaya verilen desteği ve diğer yandan ruhsal hastalığı olan kişinin yaşadığı damgalanma ve ayrımcılığın derecesi etkilerler. Bu nedenle her ülkenin kendine özgü bir bağlamı, kültürü, kaynakları ve mevcut hizmet yapıları vardır ve her biri ruh sağlığı politikalarına ihtiyaç duymaktadır (Mirza vd., 2006; Jenkins, 2008).

Sosyal refah devleti, bu tür olumsuz sosyo-ekonomik koşullar ile ruh sağlığı arasındaki bağlantıya aracılık edebilir. Örneğin, savunmasız nüfus gruplarına ayni ve nakdi yardımlar ile eğitim, barınma ve halk sağlığı politikası gibi temel kamu hizmetlerini finanse eder (Eikemo ve Bambra, 2008).

Dolayısıyla, sağlık sistemlerinin temel sosyal belirleyicilerini etkileyebilir ve giderek artan bir şekilde sağlık eşitsizliklerini önleyici adımlar atabilir. Ancak sağlıkta eşitsizlikler çoğu refah devletinde hala yaygın olarak varlığını sürdürmektedir (Bambra, 2011).

Bu nedenle, sosyal refah devletinin önemli bir rolünü temsil eden ve bir sosyal politika aracı olan sosyal güvenlik politikaları; işsizlik, engellilik ve emeklilik gibi yaşam olaylarıyla ilişkili gelir kaybına yönelik düzenlemelerle bireylerin yaşam standartlarını korumalarını sağlayabilir (Hillier-Brown vd., 2019).

Sosyal güvenlik politikası reformları hem toplumsal hem de bireysel düzeyde işleyen mekanizmalar yoluyla ruh sağlığını potansiyel olarak etkileyebilir (Lundberg ve ark., 2010).

Sosyal güvenlik politikaları, gelir eşitsizliği gibi durumlara veya sağlığın iki temel sosyal belirleyicisi olan gelir ve istihdama müdahale ederek ve bu müdahalelerin sonucu oluşacak olan maddi, psikososyal ve davranışsal yollarla ruh sağlığını etkileyebilir (Simpson vd., 2021).

Çalışmalar, sosyal güvenlik politikalarındaki değişikliklerin nüfusun ruh sağlığını etkilediğini öne sürmektedir. Örneğin, sosyal güvenlik yardımlarındaki genişlemeler hem yetişkinlerde (Evans ve Craig, 2014) hem de çocuklarda (Cooper ve Stewart, 2013) olumlu ruh sağlığı sonuçlarıyla ilişkilendirilmiştir.

Öte yandan, sosyal güvenlikteki daralmalar depresyon (Reeves vd., 2016) ve intihar (Barr vd., 2016) prevalansındaki artışla ve daha büyük ruh sağlığı eşitsizlikleriyle (Kokkinen vd., 2015) ilişkilendirilmiştir.

Ancak ruhsal hastalıkların her toplumda yaygın olarak görülmesi ve hastalıkların bireye, ailesine ve topluma büyük yükü olmasına rağmen dünyada ruh sağlığı alanına gerekli önem verilmemektedir (Saxena vd., 2013).

Sağlık politika ve programlarında ruh sağlığına yeterince önem verilmemesi, personel yetersizliği, hastalıklar hakkında bilgi eksikliği nedeniyle ruhsal hastalıkların yeterince tanınamaması, ruh sağlığı hastalarına karşı damgalama ve ayrımcılık olması ve hastaların yaşadığı çevrede ruh sağlığı hizmeti sunan kurumların bulunmaması ve mevcut tedavi kurumlarına da ulaşımın zor olması nedeni ile ruh sağlığı hastaları ihtiyacı olan bakımı alamamaktadır (World Health Organization, 2001).

Dünya Sağlık Örgütü, ülkelere ruh sağlığı alanında politika ve programlar geliştirmelerini, ruh sağlığı yasası oluşturmalarını, ruh sağlığı alanındaki politika, program ve yasal düzenlemelerin oluşturulması sürecinde toplumun, ailelerin ve hizmeti kullananların etkin bir şekilde katılmasını, ruh sağlığı hizmetlerinin birinci basamak sağlık hizmetlerine entegrasyonunun sağlanmasını, sağlık hizmetlerinin tüm basamağında önemli psikotrop ilaçların ulaşılabilirliğinin sağlanmasını, bireyin ihtiyacı olan hizmetleri kolayca alabilmesi için ruh sağlığı hizmetlerinin akıl hastaneleri yerine bireyin yaşadığı çevrede verilmesini, sağlık personelinin ruhsal hastalıklar konusunda eğitilmesini, ruh sağlığı alanında çalışanların sayılarının arttırılmasını, ruh sağlığı hastalarının damgalanmasına karşı çalışmalar yapmalarını ve ruh sağlığına bütüncül bir şekilde yaklaşarak eğitim, belediye ve sosyal hizmetler gibi diğer sektörlerle iş birliği yapılmasını tavsiye etmiştir (World Health Organization, 2001).

Ruh sağlığını korumak ve iyileştirmek, çoklu kararları içeren karmaşık bir görevdir. Sosyal politika; ruh sağlığı ihtiyaçları, koşulları, hizmetleri, tedavileri ve önleme ve teşvik stratejileri ile bunların finansmanı konusundaki yapılacak seçimler arasında önceliklerin belirlenmesini gerektirir. Ruh sağlığı hizmetleri ve stratejileri kendi aralarında ve sosyal güvenlik, eğitim, istihdam ve barınma gibi diğer hizmetlerle iyi koordine edilmelidir. Kararların mevcut zorlukları karşılayacak şekilde sürekli olarak ayarlanabilmesi için ruh sağlığı sonuçları izlenmeli ve analiz edilmelidir. Yönetimde kritik rol; karmaşık faaliyetlerin gerçekleştirilmesini sağlamak için sorumluluğu üstlenmek, politika geliştirmek ve uygulamaktır. Politika; temel konuları ve hedefleri belirler, finansman ve tedarikte kamu ve özel sektörün ilgili rollerini tanımlar, ruh sağlığı hedeflerini karşılamak için kamuda ve özel sektörde gerekli politika araçlarını ve düzenlemeleri yapar, kapasite belirler, bina ve organizasyonel gelişim ve harcamaların önceliklendirilmesi için rehberlik sağlar, sorunların analizini yapar ve sonuca bağlar ve kaynak tahsisi ile ilgili kararları alır (World Health Organization, 2021).

Ruh sağlığı ve sosyal politika arasındaki ilişkinin boyutlarına dair bilgiler, (Flatau vd., 2000; Mathers ve Loncar, 2006; Mirza vd., 2006; Gureje ve Jenkins, 2007; Eikemo ve Bambra, 2008; Jenkins, 2008; Saxena vd., 2013; Silva vd., 2016; Turnpenny vd.,

2018; Hillier-Brown vd., 2019; Simpson vd., 2021; World Health Organization, 2021) aşağıda belirtildiği şekilde özetlenebilir:

1. Ruh sağlığı politikalarının belirlenmesi: Ruh sağlığı politikaları, bir ülke veya toplumun ruh sağlığına yönelik nasıl yaklaşımda bulunulması gerektiğini belirler. Bu politikalar, toplumun genel refahını artırmak ve psikolojik sağlığını desteklemek amacıyla oluşturulur. Sosyal politikalar, ruh sağlığı politikalarının oluşturulmasında etkin rol alabilir.

2. Erişilebilir ruh sağlığı hizmetleri: Sosyal politikalar, ruh sağlığı hizmetlerine ulaşımı kolaylaştırır. Özellikle düşük gelirli bireyler veya dezavantajlı gruplar için bu hizmetlere erişimin arttırılması, sosyal politikanın bir parçası olabilir.

3. Erişilebilir ve Kapsayıcı Ruh Sağlığı Hizmetleri: Sosyal politikalar, ruh sağlığı hizmetlerine erişimin artırılmasını ve bu hizmetlerin kapsayıcı olmasını sağlamalıdır. Özellikle dezavantajlı grupların (örneğin, engelliler, mülteciler, düşük gelirli bireyler) ruh sağlığı hizmetlerine erişimini kolaylaştıran politikalar geliştirilmelidir.

4. Entegre Yaklaşım ve İşbirliği: Ruh sağlığı politikalarının etkinliği, diğer sosyal politika alanlarıyla işbirliği içinde geliştirilmesine bağlıdır. Örneğin, sağlık, eğitim, istihdam ve sosyal hizmetler arasında entegrasyon sağlanarak, bireylerin çok yönlü desteklenmesi mümkündür.

5. Toplumsal bilinçlenmenin artırılması ve damgalanmanın azaltılması: Ruh sağlığı hakkında toplumsal bilginin arttırılması ve damgalanmanın azaltılmasında sosyal politikaların rolü büyüktür. Bu rol, bireylerin ruh sağlığı hizmetlerine açıkça ve utanmadan başvurmalarını teşvik edebilir, ayrımcılığı azaltabilir ve toplumun ruh sağlığı hakkında doğru bilgilere sahip olmasında etkili olabilir.

6. Kriz durumlarına ve acil durumlara hazırlık: Sosyal politikalar, toplumsal krizler veya doğal afetler gibi olağanüstü durumlarda ruh sağlığının etkinliğini ve sürdürülmesini sağlayabilir, müdahalelere yönelik stratejiler geliştirebilir.

7. Barınma ve Yaşam Koşulları: Barınma ve yaşam koşulları, bireylerin ruh sağlığını doğrudan etkileyen faktörlerdir. Sosyal politikalar aracılığıyla sağlanan uygun barınma koşulları ve yaşam standartları, bireylerin ruh sağlığını korumada önemli bir rol oynar.

8. Eğitim ve farkındalık: Ruh sağlığına yönelik eğitim ve standart kampanyalar, sosyal politikaların bir parçası olarak uygulanabilir. Bu durum bireylerin ruh sağlığına daha iyi bir şekilde dikkat etmelerini sağlayabilir ve yardım aramalarını teşvik edebilir.

9. Eğitim ve İstihdam: Eğitim ve istihdam politikaları, bireylerin ruh sağlığını doğrudan etkileyebilir. Eğitimde fırsat eşitliği sağlanması ve işsizlik oranlarının düşürülmesi, bireylerin kendilerini güvende hissetmelerine ve psikolojik iyilik hallerinin korunmasına katkıda bulunur.

10. Sosyal yardım ve destek programları: Sosyal politikalar, ekonomik zorluklarla karşılaşan bireylere ve ailelere mali yardım ve destek sunabilir. Bu durum, stresi yönetimini ve ruh sağlığını iyileştirebilir.

11. Sosyal Güvenlik ve Destek: Sosyal güvenlik ve destek mekanizmaları, özellikle ekonomik sıkıntı yaşayan bireyler için ruh sağlığını destekleyici bir rol oynar. Örneğin, sosyal yardımlar ve sağlık sigortası gibi uygulamalar, bireylerin stres seviyelerini azaltarak ruh sağlığını iyileştirebilir.

12. Toplumsal uyumu destekleme: İyi bir ruh sağlığına sahip bireyler, toplumsal sürdürülebilirliği sağlayabilirler. Sosyal politikalar, toplumsal kalkınmayı teşvik etmek ve sosyal çatışmaları azaltmak için ruh sağlığına odaklanabilir.

13. Bireylerin ruh sağlığı sorunlarıyla başa çıkma yeteneklerini güçlendirme: Sosyal politikalar bireylerin; stresle başa çıkma, problem çözme ve duygusal becerileri geliştirmelerine yardımcı olabilir. Bu, ruhsal durumun korunması için önemlidir.

14. Eşitsizliklerle mücadele etme: Eşitsizlikler, bireylerin ruhsal sorunlar yaşamasına neden olabilir. Örneğin, düşük gelirli ailelerin ekonomik yönden daha savunmasız olmaları nedeniyle ruh sağlığı sorunları geliştirme riski olabilir. Sosyal politikalar, ekonomik koşullar ile ruh sağlığı arasındaki bağlantıya aracılık edebilir.

15. Önleyici hizmetler: Sosyal politikalar, önleyici hizmetleri teşvik edebilir. Örneğin, erken çocukluk dönemlerinde çocuklara ve ailelere yönelik sağlık ve eğitim programlarını destekleyerek ilerleyen yaşlarda ortaya çıkabilecek ruhsal sağlık sorunlarının önlenmesine yardımcı olabilir.

16. Önleyici Tedbirler ve Eğitim Programları: Sosyal politika kapsamında, ruh sağlığını koruyucu ve önleyici tedbirler alınmalıdır. Bu kapsamda, okullarda ve iş yerlerinde ruh sağlığı eğitim programları düzenlenmeli, stres yönetimi ve duygusal zeka gibi konularda farkındalık artırılmalıdır.

17. Politika Entegrasyonu: Ruh sağlığı politikalarının sosyal politikalarla entegre edilmesi, kapsamlı ve bütüncül bir yaklaşım sağlar.

18. Kaynakların Etkin Kullanımı: Sosyal politika alanında ayrılan kaynakların, ruh sağlığı hizmetleri için de kullanılabilmesi, hizmetlerin erişilebilirliğini artırır.

19. Toplumsal Farkındalık: Hem ruh sağlığı hem de sosyal politika alanında farkındalık kampanyalarının yürütülmesi, toplumun bilinçlenmesine ve stigma ile mücadelede etkili olabilir.

20. Çocuk ve gençlerin ruh sağlığı: Çocukların ve gençlerin ruhsal sağlığı, geleceğin toplumunun temeli olması nedeniyle

sosyal politikaların çocuklara ve gençlere yönelik ruhsal sağlık hizmetlerinin desteklenmesi önemlidir.

21. Toplumsal refahın artırılması: Sosyal politikalar, toplumun genel refahını artırmayı amaçlamaktadır. Bu amaç; sağlık hizmetleri, eğitim ve istihdam gibi temel özellikleri içermektedir. Ruh sağlığı da bu genel refahın bir parçasıdır; çünkü psikolojik olarak iyi oluş, toplumsal refahın önemli bir bileşenidir.

Ruh sağlığı ve sosyal politika; ruh sağlığına yönelik uygulamaları yaygınlaştırma, toplumun genel refahını artırma, bireylerin psikolojik yönden iyi oluşunu sağlama ve ruh sağlığını koruma yönlerinden güçlü bir şekilde birbirine bağlıdır. Ruh sağlığını iyileştirmeye yönelik etkili sosyal politikalar; toplumun daha sağlıklı, huzurlu ve üretken olmasına katkıda bulunabilir.

Diğer taraftan sosyal politikanın temel amacı ise; sosyal uyum, sosyal denge, düzen ve istikrarı sağlamaktır. Bunun yanı sıra birey ve toplumun refahını ve hayat standardını geliştirmeyi ve korumayı hedefler. Toplumsal düzen, uyum ve istikrar, ruhsal yönden sağlıklı ve sosyal işlevselliği yerinde olan bireylerle mümkündür.

Sosyal destek ve sosyal bakım ruh sağlığının ve ruh sağlığı hizmetlerinin ana bileşenidir ve hayati öneme haizdir. Örneğin engelli bireylerin (genellikle psikiyatrik hastalıkların da eşlik ettiği komorbitide) koruma altına alındığı ASHB bünyesindeki Bakım ve Rehabilitasyon Merkezleri hem sosyal hizmetin hem de sosyal politikanın primer düzeyde ilgi ve sorumluluk alanındadır. Bu örnekten de anlaşılacağı üzere ruh sağlığı ve sosyal politika arasındaki yapısal ve fonksiyonel bir ilişkinin varlığı ontolojik bir gerçekliktir. Başka bir deyişle ruh sağlığı politikaları ile sosyal politika arasındaki ilişki zorunlu bir sonuçtur.

Ruh sağlığı alanına ilişkin stigmatizasyon (damgalama) aynı zamanda önemli bir sosyal sorundur. Stigmatizasyonun azaltılması ve bu sorunla mücadelede sosyal politika faaliyetleri önem arz etmektedir.

Sağlık: hastalık ve sakatlığın olmayışı değil aynı zamanda biyolojik, psikolojik ve sosyal yönden tam bir iyilik halidir (WHO). Tanımdan da anlaşılacağı üzere psikolojik iyilik hali ve ruh sağlığı, sağlığın ana bileşenleridir ve sosyal yönden iyilik hali de sağlığın yadsınamaz ana unsurlarındandır. Sağlık ise sosyal politikanın yapısal ve işlevsel ögelerinden, organlarından biridir. Bu yönüyle de ruh sağlığı ile sosyal politika arasında organik bir ilişkinin varlığı kendiliğinden açığa çıkmaktadır.

Bunlarla birlikte ruh sağlığı hizmet sürecinde hizmet alanlar ve hizmet verenlerin sosyal sigortaları ve sağlık sigortaları, SGK gibi sosyal politika kurumları ile sağlanmaktadır.

Diğer taraftan istihdam ve çalışma hayatı, bireyler için sadece ekonomik kazanç elde etmek değil, aynı zamanda sosyalleşme imkanı sağlar. Sosyalleşme ve sosyal ilişkiler de ruh sağlığı için kritik öneme haiz değişkenlerdir.

Toplumsal uyum ve toplumsal düzen ruh sağlığı yerinde olan bireylerle mümkündür.

Tartışma

Ruh sağlığı ve sosyal politikalar arasındaki ilişki, bireylerin ve toplulukların refahını artırmak için kritik öneme sahiptir. Mesleki açıdan, sosyal hizmet uzmanları ve ruh sağlığı profesyonelleri, bireylerin ihtiyaçlarını karşılamak için sosyal politikalarla desteklenir. Akademik açıdan, disiplinler arası çalışmalar ve araştırmalar, ruh sağlığı hizmetlerinin geliştirilmesine katkıda bulunmaktadır. Bilimsel açıdan, ruh sağlığı epidemiyolojisi ve kanıta dayalı uygulamalar, sosyal politikaların etkinliğini artırmada rol oynamaktadır. Adalet, eşitlik ve insanın iyi olma hali, sosyal politikaların felsefi temelini oluşturmaktadır. Sağlık hakkı ve sosyal adalet ise insan hakları kuramları açısından ise ruh sağlığı hizmetlerine erişimin önemini vurgulamaktadır.

Ruh sağlığı politikaları ve sosyal politika arasındaki ilişki, bireylerin genel refahını artırmak için kritik bir öneme sahiptir. Etkili sosyal politikalar, bireylerin ruh sağlığını iyileştirerek toplumsal refahı artırabilir. Bu iki politika alanı arasındaki uyum, hem bireylerin hem de toplumun genel sağlığı ve refahı için vazgeçilmezdir. Ayrıca, ruh sağlığı politikalarının sosyal politikalarla bütünleşik bir şekilde uygulanması, toplumda ruh sağlığı sorunlarının önlenmesine ve tedavi edilmesine yönelik daha etkili çözümler sunabilir.

Ruh sağlığı, ruh sağlığı politikaları ve sosyal politika arasında güçlü ve karşılıklı bir ilişki bulunmaktadır. Etkili ruh sağlığı politikaları, bireylerin ve toplumların ruh sağlığını iyileştirirken, kapsamlı sosyal politikalar ise ruh sağlığı üzerindeki olumsuz sosyal ve ekonomik faktörleri azaltmada önemli rol oynar. Bu iki alanın entegrasyonu, toplum genelinde daha sağlıklı ve mutlu bireyler yaratmak için kritik öneme haizdir.

Ruh sağlığı politikaları, bireylerin ruh sağlığını koruma ve iyileştirme amaçlı stratejileri kapsar ve sosyal politika çerçevesinde yer alır. Bu politikaların etkin bir şekilde uygulanabilmesi için sosyal politikalarla uyumlu olması gerekmektedir.

Ruh sağlığı politikaları ve sosyal politikalar arasındaki işbirliği, şu noktalarda güçlendirilebilir:

Sağlık Hakkı

İnsan hakları kuramları, sağlığı temel bir insan hakkı olarak tanımlar. Ruh sağlığı, bu hakkın önemli bir bileşenidir. Sosyal politikalar, bireylerin ruh sağlığı hizmetlerine

erişimini sağlamak ve bu hizmetlerin kalitesini artırmak için oluşturulmalıdır. Bu bağlamda, ruh sağlığı hizmetlerine erişim, ayrımcılıktan arındırılmış ve kapsayıcı olmalıdır.

Sosyal Adalet

İnsan hakları perspektifinden bakıldığında, sosyal adalet, herkesin toplumsal kaynaklardan adil bir şekilde yararlanmasını gerektirir. Ruh sağlığı hizmetlerine erişim, sosyal adaletin bir göstergesidir. Sosyal politikalar, dezavantajlı ve marjinalize edilmiş grupların ruh sağlığı hizmetlerine erişimini artırmak için özel önlemler almalıdır.

Adalet ve Eşitlik

Ruh sağlığı ve sosyal politikalar, adalet ve eşitlik ilkelerine dayanır. Bu nedenle, herkesin ruh sağlığı hizmetlerine eşit erişim hakkına sahip olması gerekmektedir. Sosyal politikalar, bu eşitliği sağlamak için stratejiler ve programlar geliştirir. Adalet ve eşitlik, toplumdaki tüm bireylerin ruh sağlığı hizmetlerinden yararlanabilmesini güvence altına alır.

İnsanın İyi Olma Hali

İnsanın iyi olma hali, fiziksel, ruhsal ve sosyal sağlığı kapsar. Sosyal politikalar, bireylerin bütünsel iyi olma halini desteklemeyi hedefler. Bu, ruh sağlığı hizmetlerinin yanı sıra, eğitim, istihdam, barınma ve sosyal destek gibi alanlarda da kapsamlı politikaların uygulanmasını gerektirir.

Disiplinler Arası Çalışmalar

Ruh sağlığı ve sosyal politikalar, disiplinler arası çalışmalar gerektirir. Psikoloji, sosyal hizmet, sosyoloji, halk sağlığı ve siyaset bilimi gibi disiplinler, ruh sağlığı ve sosyal politikalar konusunda ortak araştırmalar ve işbirliği yapmayı gerekli kılar. Bu disiplinler arası yaklaşım, ruh sağlığı hizmetlerinin kapsamını ve işlevini artırır.

Ruh Sağlığı Epidemiyolojisi:

Ruh sağlığı epidemiyolojisi, ruh sağlığı sorunlarının yaygınlığını, dağılımını ve belirleyicilerini inceleyen bir bilim dalıdır. Bu alandaki araştırmalar, sosyal politikaların ruh sağlığı üzerindeki etkilerini anlamak için önemlidir. Örneğin, yoksulluk, işsizlik ve sosyal dışlanma gibi sosyoekonomik faktörlerin ruh sağlığı üzerindeki etkileri bilimsel olarak incelenir. Bu da psikiyatrik hastalıkların teşhis ve tedavisinde kritik rol oynar.

Kanıta Dayalı Uygulamalar:

Sosyal politikalar, ruh sağlığı alanında kanıta dayalı uygulamaları teşvik eder. Bu, ruh sağlığı hizmetlerinin etkinliğini ve verimliliğini artırmak için bilimsel araştırmalara dayalı yöntemlerin kullanılmasını içerir. Kanıta dayalı uygulamalar da sosyal hizmet uzmanlarının ve ruh sağlığı profesyonellerinin en iyi müdahale stratejilerini belirlemelerine yardımcı olur.

Sonuç

Ruh sağlığı, ruh sağlığı politikaları ve sosyal politika arasındaki ilişki, bireylerin ve toplumların genel sağlığı ve refahı açısından büyük önem taşımaktadır. Etkili ruh sağlığı politikalarının ve kapsamlı sosyal politikaların geliştirilmesi, toplumun ruh sağlığını iyileştirecek ve bireylerin daha sağlıklı, üretken ve mutlu bir yaşam sürmelerini sağlayacaktır. Gelecekte, bu iki alanın entegrasyonu ve iş birliği, toplumun genel refahını artırmada önemli bir rol oynayacaktır.

Ruh sağlığı, ruh sağlığı politikaları ve sosyal politika arasındaki ilişki, toplumsal refahın sağlanmasında önemli bir rol oynar. Sosyal politikaların, bireylerin ruh sağlığını destekleyecek şekilde tasarlanması ve ruh sağlığı politikalarının sosyal politika çerçevesine entegre edilmesi, toplumun genel sağlığı ve refahı açısından büyük önem taşır. Bu iki politika alanı arasındaki iş birliği ve entegrasyon, gelecekte daha sağlıklı ve mutlu toplumlar inşa etmek için kritik bir strateji olarak değerlendirilmelidir.

Ruh sağlığı ve sosyal hizmet arasındaki ilişki, bireylerin ve toplulukların refahını artırmayı amaçlayan bütüncül bir yaklaşıma dayanır. Sosyal hizmet uzmanları, ruh sağlığı sorunları yaşayan bireylere müdahale ve destek sunar, önleme ve bilinçlendirme çalışmaları yapar, savunuculuk yapar ve toplumsal entegrasyonu destekler. Bu ilişki, multidisipliner bir işbirliği ve koordinasyon gerektirir. Gelecekte, ruh sağlığı ve sosyal hizmet alanlarındaki işbirliğinin artırılması, toplumların genel sağlık ve refah düzeyini önemli ölçüde iyileştirecektir.

Ruh sağlığı ve sosyal politikalar arasındaki ilişki, bireylerin ve toplulukların genel refahını artırmayı amaçlayan çok yönlü ve kapsamlı bir etkileşimdir. Bu ilişki, mesleki, akademik, bilimsel, felsefi ve insan hakları kuramları açılarından incelendiğinde, ruh sağlığı hizmetlerinin ve sosyal politikaların entegrasyonunun önemi ortaya çıkmaktadır. Gelecekte, ruh sağlığı ve sosyal politikalar arasındaki işbirliğinin güçlendirilmesi, toplumların genel sağlık ve refah düzeyini önemli ölçüde iyileştirecektir.

Bu iki politika alanı, birbirleriyle güçlü bir ilişki içindedir. Özellikle bu mesleki ve akademik ilişkinin varlığı, sosyal politikanın koruyucu ve önleyici hekimlik ile sosyal destek mekanizmaları bakımından hayati öneme haiz rolüne içkin bir gerçeklik olarak öne çıkmaktadır.

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Research Article

Exploring the interplay between sociodemographic factors, clinical characteristics, and anxiety levels in cancer patients: a cross-sectional study

Kanser hastalarında sosyodemografik faktörler, klinik özellikler ve anksiyete düzeyleri arasındaki ilişki: Kesitsel bir çalışma

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Abstract

Aim: The primary aim of this study was to examine the correlation between anxiety levels and the sociodemographic and clinical characteristics in cancer patients undergoing chemotherapy. Precisely identifying patient cohorts with varying psychological responses can substantially enhance cancer treatment through the improved integration of personalized therapeutic options.

Material and Methods: A cross-sectional study involving 199 cancer patients at a medical oncology department utilized a questionnaire and the Hamilton Anxiety Scale (HAM-A) to collect sociodemographic and clinical data. Statistical analysis assessed anxiety levels and their correlation with various factors.

Results: The study included 199 cases with an average age of 57.28±11.76 years, consisting of 47.7% males and 52.3% females. Women exhibited a higher average age (55.18±1.15 years) compared to men (59.58±1.17 years). Among the participants, 165 were married, and 41.2% were high school graduates, with 67.8% not employed. Colorectal and pancreaticobiliary system tumors were most common (26.1%), while central nervous system tumors were least common (0.5%). The majority (59.3%) had metastatic cancer, and 55.8% were undergoing classical chemotherapy. The average Hamilton Anxiety Scale (HAM-A) score was 25.63±7.90, with women scoring higher than men (26.67±0.77 vs. 24.48±0.80, p=0.025). Minor anxiety was observed in 46.7%, while 53.3% experienced major anxiety. Genitourinary system tumors had the highest HAM-A score (26.08±1.54), and metastatic patients and those undergoing immunotherapy reported higher anxiety levels. No significant relationships were found between anxiety scores and sociodemographic factors, cancer type, comorbidity, cancer stage, treatment method, Eastern Cooperative Oncology Group Performance Status, or radiotherapy.

Conclusions: The study highlighted gender differences in anxiety, aligning with existing literature. Sociodemographic factors, except gender, showed no significant correlation with anxiety levels. Specific cancer types and advanced stages demonstrated higher anxiety, emphasizing the need for targeted psychosocial support. This research contributes to understanding the complex interplay between sociodemographic factors, clinical characteristics, and anxiety in cancer patients. The findings support the development of targeted interventions for specific patient groups, aligning with the broader goal of providing empathetic and comprehensive cancer care.

Keywords: Cancer, Anxiety, Hamilton Anxiety Scale (HAM-A), Sociodemographic factors

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Öz

Amaç: Bu çalışmanın temel amacı, kemoterapi gören kanser hastalarında anksiyete düzeyleri ile sosyodemografik ve klinik özellikler arasındaki ilişkiyi incelemekti. Farklı psikolojik tepkilere sahip hasta gruplarını doğru belirlemek, kişiselleştirilmiş tedavi seçeneklerinin daha iyi entegrasyonu yoluyla kanser tedavisini önemli ölçüde iyileştirebilir.

Gereç ve Yöntemler: Tıbbi onkoloji bölümünde 199 kanser hastasını içeren bu kesitsel çalışmada, Hamilton Anksiyete Ölçeği (HAM-A) anketi kullanılarak sosyodemografik ve klinik veriler toplandı. İstatistiksel analiz, anksiyete düzeylerini ve çeşitli faktörlerle olan ilişkilerini değerlendirdi.

Bulgular: Çalışma, yaş ortalaması 57.28±11.76 olan, %47.7'si erkek ve %52.3'ü kadın olan 199 vaka içeriyordu. Kadınlar, erkeklere kıyasla daha yüksek bir ortalama yaşa sahipti (sırasıyla 55.18±1.15 ve 59.58±1.17). Katılımcıların 165'i evliydi ve %41.2'si lise mezunuydu, %67.8'i ise çalışmıyordu. Kolorektal ve pankreatik-biliyer sistem tümörleri en yaygın olanıydı (%26.1), merkezi sinir sistemi tümörleri ise en az yaygın olanıydı (%0.5). Katılımcıların çoğunluğu (%59.3) metastatik kansere sahipti ve %55.8'i klasik kemoterapi alıyordu. Ortalama Hamilton Anksiyete Ölçeği (HAM-A) puanı 25.63±7.90 idi ve kadınlar, erkeklere kıyasla daha yüksek puan aldı (%26.67±0.77 ve %24.48±0.80, p=0.025). Katılımcıların %46.7'sinde hafif anksiyete gözlemlendi, %53.3'ünde ise ciddi anksiyete yaşandı. Genitoüriner sistem tümörleri en yüksek HAM-A puanına sahipti (%26.08±1.54), metastatik hastalar ve immünoterapi alanlar daha yüksek anksiyete seviyelerini bildirdi. Anksiyete puanları ile sosyodemografik faktörler, kanser türü, eşlik eden hastalıklar, kanser evresi, tedavi yöntemi, Eastern Cooperative Oncology Group Performans Durumu veya radyoterapi arasında anlamlı bir ilişki bulunamadı.

Sonuçlar: Çalışma, anksiyetede cinsiyet farklılıklarını vurgulayarak mevcut literatürle uyumludur. Cinsiyet dışındaki sosyodemografik faktörlerin anksiyete seviyeleriyle anlamlı bir ilişkisinin olmadığı ortaya çıkmıştır. Belirli kanser türleri ve ileri evreler daha yüksek anksiyete göstermiştir, psikososyal destek ihtiyacının özellikle bu gruptaki hastalarda desteklenmesini gerektirir. Bu araştırma, kanser hastalarında sosyodemografik faktörler, klinik özellikler ve anksiyete arasındaki karmaşık etkileşimi anlamamıza katkı sağlamaktadır.

Anahtar Kelimeler: Kanser, anksiyete, Hamilton Anksiyete Ölçeği (HAM-A), sosyodemografik faktörler

Introduction

Cancer, a formidable adversary to physical health, introduces a profound emotional upheaval for those affected. The journey from cancer diagnosis to treatment encompasses a spectrum of psychological responses, shaping the overall experience of individuals facing this formidable challenge. Understanding the intricate interplay between cancer diagnosis and the psychological aspects of this profound moment is essential for providing holistic and patient-centered care.

Receiving a cancer diagnosis is a pivotal moment in an individual's life, often marked by an influx of emotions ranging from shock and fear to uncertainty and anxiety. The impact of this revelation extends beyond the physical realm, reaching deep into the psychological and emotional core of the individual. Each patient's response to a cancer diagnosis is a unique and personal experience, influenced by various factors, including the type and stage of cancer, individual coping mechanisms, and the availability of a robust support system.

The emotional impact of a cancer diagnosis extends beyond the immediate shock, encompassing long-term psychological aspects that influence coping mechanisms, treatment adherence, and overall quality of life. The significance of understanding these psychological dimensions lies in the potential to tailor interventions and support systems that address the unique needs of each patient.

In this exploration, we delve into the existing literature, drawing on both quantitative and qualitative insights, to paint a comprehensive picture of the psychological responses observed in cancer patients post-diagnosis. By shedding light on these psychological aspects, we aim to contribute to the growing body of knowledge that informs healthcare professionals, researchers, and policymakers about the intricate nuances of cancer care.

The comprehensive review conducted by Dinapoli L. et al. highlights the prevalence of anxiety, distress, depression, and posttraumatic stress disorder among breast cancer patients, emphasizing the need for ongoing psychotherapeutic and supportive interventions throughout the oncological journey

[1]. Numerous studies conducted on patients monitored with various cancer diagnoses have investigated psychological disorders, including depression and anxiety [2,3,4,5].

In a study conducted by Naser and colleagues on anxiety and cancer, it was concluded that the prevalence of anxiety approaches 50%, particularly in cancers with high incidence rates such as lung, prostate, and breast cancer [6]. Additionally, 15% of these patients required supplementary medical treatments for the management of anxiety [6]. In a large multicenter cohort study conducted by Goerling and colleagues on the frequency and severity of anxiety in cancer patients, it was demonstrated that the risk of anxiety significantly increases in cancer patients. Furthermore, the study emphasized the importance of the challenges in managing anxiety in patients with advanced-stage cancer [7]. In a study conducted by Vitale and colleagues evaluating the relationship between anxiety and depression in cancer patients and gender differences, it was found that women are more open to expressing their experiences with anxiety and depression compared to men [8]. However, the rate of anxiety among men was also notably high [8]. The study demonstrated that anxiety impacts daily life and poses challenges in treatment for both genders [8].

Building upon this foundation, our study seeks to establish a framework for a compassionate, patient-centric care model. This model aims to address not only the physiological manifestations of the disease but also its emotional dimensions, thereby acknowledging and comprehending the psychological complexities linked with a cancer diagnosis.

Material and Methods

This study was conducted following the approval granted by the Ethics Committee of Health Sciences University Antalya Training and Research Hospital, as per the decision numbered 315/2023 dated 29.10.2023.The study involved 220 participants aged 18-75, who sought care at the Medical Oncology Department of Health Sciences University Antalya Training and Research Hospital between 02.11.2023-03.12.2023 and who provided informed consent. Twenty-one participants were excluded from the study due to missing data.

For data collection, a questionnaire encompassing socio-demographic and clinical information and the Hamilton Anxiety Scale (HAM-A) were administered to individuals admitted to the Medical Oncology Department of the Hospital. The socio-demographic survey form included questions about age, gender, education level, marital status, employment status, income level, and smoking status. The clinical data survey form inquired about comorbidities, cancer type, cancer stage at diagnosis, the treatment administered, and whether radiotherapy was applied.

The HAM-A scale, utilized to assess anxiety levels and symptom distribution, comprises 14 questions measuring both physical and psychological symptoms, utilizing a five-point Likert-type scale [9]. The total score ranges from 0 to 56, with each question scored between 0 and 4. Scores of 0-5 indicate no anxiety, 6-14 indicate minor (mild-moderate) anxiety, and 15 and above indicate major (severe) anxiety [10].

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 27 (SPSS Inc., Chicago, IL). Continuous variables are presented as median, mean ± standard deviation, while categorical variables are expressed as numbers and percentages. Normal distribution was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Data conforming to normal distribution were compared using the Student T test, while the Mann Whitney U and Kruskal Wallis tests were employed for data not complying with normal distribution. Results with a p-value below 0.05 were considered statistically significant.

Results

The average age of the 199 cases who applied to the Medical Oncology department was 57.28±11.76 years. Ninety-five (47.7%) of the cases were male, and 104 (52.3%) were female. The average age of women in the study was 55.18±1.15 years, while the average age of men was 59.58±1.17 years. One hundred sixty-five cases were married, and among them, 163 had children. Among the cases participating in the study, 41.2% were high school graduates, and 67.8% were not working. Ninety-four percent of the cases in the study resided in Antalya. Table 1 summarizes the sociodemographic data of the cases.

In our study, colorectal and pancreaticobiliary system tumors were the most frequently observed (26.1%), while central nervous system tumors were the least common (0.5%).While 118 (59.3%) of the cases were metastatic patients, 111 (55.8%) were undergoing classical chemotherapy treatment. ECOG PS was 1 in 150 cases (75.4%). Table 1 summarizes the clinical data of the cases.

The average HAM-A score for the cases in our study was 25.63±7.90. The average HAM-A score was 26.67±0.77 in

women and 24.48±0.80 in men. When categorizing anxiety into minor (mild-moderate) and major (severe) based on the HAM-A scale. According to the HAM-A scale, 93 cases (46.7%) exhibited minor anxiety, while 106 cases (53.3%) had major anxiety.

The HAM-A score average was found to be higher in women than in men, and a statistically significant difference was found between them (p=0.025). There was no significant difference between sociodemographic data such as educational status, marital status, income status, occupational status, presence of children, and living alone and HAM-A score averages (p>0.05). Table 1 summarizes the sociodemographic data along with the HAM-A score averages (anxiety levels) of the patients. Among different cancer types, the highest average Ham A score was found in genitourinary system tumors (26.08±1.54), while the lowest was observed in colorectal and pancreatic/biliary system tumors (22.96±0.97). Metastatic patients were found to have higher anxiety than early-stage patients. Higher anxiety was found in those receiving immunotherapy treatment compared to other types of treatment. No significant relationship was found between age, cancer type, smoking status, comorbidity, cancer stage at diagnosis, treatment method used, ECOG PS, and radiotherapy treatment, and HAM-A score averages (p > 0.05). Table 2 summarizes the clinical data along with the HAM-A score averages (anxiety levels) of the patients.

Table 1. The distribution of sociodemographic characteristics among the patients and their association with anxiety levels.

Categorical features	n(%)	HAM-A score average	p value
Educational Background			
Illiterate	41(20.6%)	27.39±1.02	0.051
Primary school	64(32.2%)	25.47±0.88	
High school	82(41.2%)	25.46±1.01	
University	12(6.0%)	21.58±1±80	
Marital status			
Married	165 (82.9%)	25.75±0.61	0.369
Single	34 (17.1%)	25.03±1.44	
Child			
Yes	36(18.1%)	26.06±0.63	0.078
No	163(81.9%)	23.67±1.16	
Professional status			
Working	64(32.2%)	24.84±1.03	0.160
Not working	135(67.8%)	26.0±0.66	
Income Status			
Low	23(11.6%)	26.04±1.60	0.680
Modarate	132(66.3%)	26.05±0.68	
High	44(22.1%)	24.66±1.23	

Abbreviations: HAM-A; Hamilton Anxiety Rating Scale, statistical significance; (P <0.05)

Table 2. The distribution of clinical characteristics among the patients and their correlation with anxiety levels.

Categorical features	n(%)	HAM-A score average	p value
Age (year)			
<58	95 (47.7%)	26.23±0.81	0.239
≥ 58	104 (52.3%)	25.08±0.78	
Gender			
Female	104 (52.3%)	26.67±0.77	0.025
Male	95 (47.7%)	24.48±0.80	
Smoking			
No	129 (64.8%)	25.97±0.72	0.330
Yes	70 (35.2%)	25.0±0.88	
Comorbidity			
No	153 (76.9%)	25.65±0.63	0.803
Yes	46 (23.1%)	25.57±1.25	
ECOG PS			
0	49 (24.6%)	26.02±1.15	0.689
1	150 (75.4%)	25.5±0.64	
Cancer type			
Lung cancer	43 (21.6%)	27.46±1.42	0.082
Breast cancer	54 (27.1%)	27.55±1.05	
Prostate cancer	8 (4%)	27.88±2.97	
Colorectal and pancreati-cobiliary cancer	52 (26.1)	22.97±1.00	
Genitourınary cancer	12 (6%)	26.08±1.54	
Gynecologic cancer	16 (8%)	24.63±1.84	
Head and neck cancer	11 (5.5%)	24.36±2.43	
Central Nervous System cancer	3 (3.7)	25.00±2.00	
Cancer stage at diagnosis			
Early stage	81 (40.7%)	24.70±0.93	0.301
Metastatic stage	118 (59.3%)	26.26±0.69	
Treatment received			
Classical chemotherapies	111 (55.8%)	25.34±0.78	0.352
Immunotherapy	21 (10.6%)	29.0±1.97	
Chemotherapy + immu-notherapy	22 (11.1%)	25.45±1.71	
Smart drugs	6 (3.0%)	26.33±1.76	
Chemotherapy + smart drugs	39 (19.6%)	24.62±1.01	
Radiotherapy treatment			
No	181 (91.0%)	25.85±0.59	0.388
Yes	18 (9.0%)	23.44±1.89	

Abbreviations: ECOG PS; Eastern Collaborative Oncology Group performance status, HAM-A; Hamilton Anxiety Rating Scale, statistical significance; (P <0.05)

Discussion

The results of our study shed light on the intricate relationship between cancer diagnosis, socio-demographic factors, clinical

characteristics, and anxiety levels in patients undergoing cancer treatment. The journey from cancer diagnosis to treatment is a multifaceted experience that profoundly influences the psychological well-being of individuals. Understanding the nuanced aspects of this experience is crucial for developing comprehensive and patient-centered care strategies.

Our findings revealed that gender significantly correlates with anxiety levels, with women exhibiting higher anxiety scores compared to men. A study in newly diagnosed cancer patients conducted in Iran found that anxiety was more common in women [11], while a study in operated lung cancer patients found that anxiety was more common in women [12]. In a study conducted in Germany in young cancer patients, anxiety was more common in women [13]. This aligns with existing literature indicating that gender can play a role in the emotional responses to a cancer diagnosis [14,15,16]. However, other sociodemographic factors such as age, educational background, marital status, employment status, income level, and smoking status did not show significant correlations with anxiety levels. This suggests that while gender may be a notable factor, the impact of other sociodemographic variables on anxiety levels may be more complex and multifactorial.

The type of cancer and its stage at diagnosis emerged as important factors influencing anxiety levels [14]. Breast cancer patients and those diagnosed at advanced stages exhibited higher anxiety scores. This underscores the need for tailored psychosocial support for individuals facing specific cancer types or advanced disease stages. Additionally, our study found that metastatic patients and those undergoing immunotherapy treatment reported higher anxiety levels. This emphasizes the emotional toll associated with the severity of the disease and certain treatment modalities.

The recognition of these associations holds implications for the development of patient-centered care strategies. Musical interventions, nurse-led educational interventions, using mindfulness-based stress reduction techniques have been shown to lower anxiety levels in cancer patients [17,18,19]. Tailoring interventions based on gender, cancer type, and disease stage can optimize the effectiveness of support systems. Psychosocial interventions focusing on anxiety management should be integrated into the overall cancer care plan, with particular attention to high-risk groups identified in this study.

Despite valuable insights gained, the current study has certain limitations. Due to its cross-sectional design, there are constraints in establishing causal relationships, and the focus on a specific seasonal period may affect generalizability. Similar to many studies inferring higher levels of emotional stress among advanced cancer patients, it should be noted that variable circumstances regarding cancer screening and early diagnosis awareness among the population where the study was conducted could influence the outcomes. In the future, there is a critical need for comprehensive research based on larger cohorts and long-term follow-up regarding the relationship between cancer and anxiety.

Conclusion

This study contributes to the growing body of knowledge on the psychological aspects of cancer care. By understanding the interplay between sociodemographic factors, clinical characteristics, and anxiety levels, healthcare professionals can enhance the development of targeted interventions that address the unique needs of cancer patients. This holistic approach aligns with the broader goal of providing empathetic and comprehensive care that extends beyond the physical aspects of the disease.

Declaration of conflicting interests

The authors declare no potential conflicts of interest regarding the research, authorship, or publication of this study.

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Ethics Statement

This study was approved by the Institutional Review Board of Health Sciences University Antalya Training and Research Hospital and Antalya Provincial Health Directorate (Approval Number: 2023/315). Before initiating the study, written informed consent was obtained from all participants.

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Araştırma Makalesi

KOAH atak ile acil servise başvuran hastalarda akut solunum yolu enfeksiyonlarını belirlemede ve antibiyotik başlamada prokalsitoninin önemi

The importance of procalcitonin in determining acute respiratory tract infections and initiating antibiotics in patients admitting to the emergency department with a COPD attack

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Öz

Amaç: KOAH, hava yollarının ve alveollerin hasarı sonucu kalıcı hava akımı kısıtlılığı ve solunum zorluğu ile karakterize; dünya çapında mortalite ve morbidite ile ilişkili bir hastalıktır. Bakteriyel patojenlerin KOAH alevlenmesinde ana nedenlerden biri olduğu kabul edilse de birçok hastada kesin neden tespit edilemediği için asıl nedene yönelik tedavi oldukça zor olabilmektedir. Prokalsitonin kılavuzluğunda, antibiyotik tedavisinin KOAH alevlenme hastalarının tedavisinde güvenilir bir klinik fayda sağlayıp sağlanmadığı belirsizliği devam etmektedir. Bu çalışmamızda, acil servise başvuran KOAH alevlenme hastalarında hem tanı hem de antibiyotik tedavisini belirlemede PCT'nin öngörü başarısını tespit etmeyi amaçladık.

Gereç ve Yöntemler: Çalışmamız tek merkezli ve prospektif olarak planlandı. Çalışma, hastanemiz acil servisine KOAH alevlenme ile başvuran ve çalışmaya dahil edilme kriterlerini karşılayan ve geliş sırasına göre randomize olarak seçilen 100 hasta ile yapıldı.

Bulgular: Çalışmamıza dahil edilen 100 hastanın %87'si erkek ve yaş ortalaması 70,4±10,5 yıl idi. PCT ve CRP düzeylerine göre verilen tedavi ve sonlanım değerlendirildiğinde; antibiyotik başlanan olgular ile başlanmayan olgular arasında CRP ve PCT ortanca değerleri arasında anlamlı fark olduğu tespit edildi (sırasıyla $p=0.017$ ve $p<0.001$). Taburculuktan servis yatışına ve servis yatışından yoğum bakım ünitesine yatışa doğru gidildiğinde (hastanın kritikliği arttığında) PCT'nin de anlamlı olarak yüksek olduğu görüldü ($p<0.001$). Fakat sonlanım ile CRP arasındaki bu ilişki anlamlı farklı değildi.

Sonuç: KOAH atak nedeniyle acil servise başvuran hastalarda prokalsitonin; hastalığın şiddeti, antibiyotik başlanma kararı, NIMV ve IMV tedavisine, hastaların Acil Servis'ten taburculuk veya hastaneye kabulünü belirleyen önemli bir belirteç olduğu düşünüyoruz.

Anahtar Kelimeler: Kronik Obstrüktif Akciğer Hastalığı, Akut Atak, Antibiyotik Yönetimi, İnflamatuar Biyobelirteçler

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Abstract

Aim: COPD is characterized by permanent airflow limitation and difficulty breathing as a result of damage to the airways and alveoli; It is a disease associated with mortality and morbidity worldwide. Although it is accepted that bacterial pathogens are one of the main causes of COPD exacerbation, treatment for the main cause can be quite difficult since the exact cause cannot be determined in many patients. It remains unclear whether procalcitonin-guided antibiotic therapy provides a reliable clinical benefit in the treatment of patients with COPD exacerbations. In this study, we aimed to determine the predictive success of PCT in determining both diagnosis and antibiotic treatment in COPD exacerbation patients presenting to the emergency department.

Material and Methods: Our study was planned single-center and prospectively. The study was conducted with 100 patients who presented to our hospital's emergency department with COPD exacerbation and met the inclusion criteria and were randomly selected according to the order of arrival.

Results: 87% of the 100 patients included in our study were male and the average age was 70.4±10.5 years. When the treatment and outcome are evaluated according to PCT and CRP levels; It was determined that there was a significant difference in the median values of CRP and PCT between the cases in which antibiotics were started and those in which antibiotics were not started ($p=0.017$ and $p<0.001$, respectively). It was observed that PCT was significantly higher as the patient moved from discharge to ward admission and from ward admission to intensive care unit admission (when the criticality of the patient increased) ($p<0.001$). However, this relationship between outcome and CRP was not significantly different.

Conclusions: Procalcitonin in patients admitted to the emergency department due to COPD attack; We think that the severity of the disease, the decision to start antibiotics, NIMV and IMV treatment are important indicators that determine the discharge of patients from the Emergency Department or admission to the hospital.

Keywords: Chronic Obstructive Pulmonary Disease, Acute Attact, Antibiotic Stewardship, Inflammatory Biomarkers

Giriş

Kronik obstrüktif akciğer hastalığı (KOAH) sık görülen, önlenebilir ve tedavi edilebilir bir hastalıktır. KOAH, hava yollarının ve alveollerin hasarı sonucu kalıcı hava akımı kısıtlılığı ve solunum zorluğu ile karakterize; dünya çapında mortalite ve morbidite ile ilişkili bir hastalıktır [1]. KOAH, ara ara alevlenme atakları sahip ve bu alevlenmeler sırasında akut tedaviye ve hospitalizasyona ihtiyaç duyabilmektedir. KOAH ile ilişkili bu alevlenmeler, viral ve/veya bakteriyel patojenlerden kaynaklı enfeksiyonlarda ya da hava kirliliği gibi birçok faktörden kaynaklanabilmektedir [2]. Bakteriyel patojenlerin KOAH alevlenmesinde ana nedenlerden biri olduğu kabul edilse de birçok hastada kesin neden tespit edilemediği için asıl nedene yönelik tedavi oldukça zor olabilmektedir [3].

Bakteriyel ajanların neden olduğu KOAH alevlenmelerinde birinci yaklaşımın antibiyotik tedavisi olduğu bilinmektedir. Hatta bazı çalışmalarda; antibiyotiğin KOAH alevlenme tedavilerinde başarısızlık riskini azalttığını ve yoğun bakım ünitesinde mortaliteyi azalttığını bildirmektedir [4,5]. Fakat; uluslararası kılavuzlarda, antibiyotik kullanımının yalnızca artmış nefes darlığı olan (artmış balgam pürülansı, öksürük, hırıltı ve solunum sıkıntısı durumunda) hastalarda ve non-invaziv ihtiyacı olan hastalarda kullanılmasını önermektedir [1,4,5]. Bazı çalışmalarda ise; KOAH alevlenmede, hastaların antibiyotik tedavisinden fayda görmeyebileceği bildirilmektedir [6]. Tedavideki mevcut stratejilerin, antibiyotik tedavisinin aşırı kullanımının ve özellikle KOAH alevlenmesi olan hastalarda tıbbi maliyetlerin artmasına; hastane kalış sürelerinin uzamasına ve hastane mortalite oranlarının artması bu duruma neden olarak bildirilmektedir [7-9]. Fakat, bakteriyel olan ve olmayan bir nedene sahip hastalarda hem etiyolojik nedenin net olarak tespit edilememesi hem de klinik olarak semptomların örtüşüyor olması sebebiyle antibiyotik tedavisinin kararı oldukça zor olabilmektedir [10,11].

Son zamanlarda, bakteriyel enfeksiyonlarda konakçı yanıtını belirlemek için prokalsitonin (PCT) kullanımı oldukça artmıştır. Hatta akut solunum yolu enfeksiyonu ve sepsiste antibiyotik tedavisi başlamada rehberlik etmesi, ABD Gıda ve İlaç Dairesi tarafından onaylanmıştır [12]. Fakat bu kararda etkili olan bazı randomize kontrollü çalışmaların sınırlamaları göz önüne alındığında; PCT'nin kılavuzluğunda, antibiyotik tedavisinin KOAH alevlenme hastalarının tedavisinde güvenilir bir klinik

fayda sağlayıp sağlanmadığı belirsizliği devam etmektedir. Bunun yanı sıra; mevcut çalışmaların yetersizliği nedeniyle ve mevcut GOLD kılavuzunun halen KOAH alevlenme hastalarının tedavisinde antibiyotik reçete edilmesini önermektedir [7].

Bu çalışmamızda, acil servise başvuran KOAH alevlenme hastalarında hem tanı hem de antibiyotik tedavisini belirlemede PCT'nin öngörü başarısını tespit etmeyi ve literatüre katkı sağlamayı amaçladık.

Gereç ve Yöntemler

Çalışma yeri ve çalışma popülasyonu

Çalışmamız tek merkezli ve prospektif olarak yapıldı. Çalışma, hastanemiz acil servisine KOAH alevlenme ile başvuran ve çalışmaya dahil edilme kriterlerini karşılayan ve geliş sırasına göre randomize olarak seçilen100 hasta ile yapıldı. Çalışmamızda, solunum yolu enfeksiyonu dışında bir enfeksiyonu olan, başvurusu sırasında antibiyotik kullanan, sonlanımı takip edilemeyen, çalışmaya katılmaya gönüllü oluru vermeyen ve 18 yaş altı hastalar çalışma dışı bırakıldı. Ayrıca, mükerrer başvurusu olan hastaların ilk başvurusu kullanıldı.

KOAH akut alevlenme tanısı 2015 KOAH Gold rehberinde belirtilen, "hastanın solunum semptomlarının, nefes darlığının, öksürük ve/veya balgamın normalden daha fazla kötüleşmesi ve ilaçlarında değişiklik gerektirmesi ile karakterize klinik" şeklindeki kliniğin [7] hastalarda olması ile akut alevlenme tanısı konuldu ve bu tanı alanında en az 3 yıl deneyimli göğüs hastalıkları uzmanı tarafından doğrulandı.

Veri toplama

Çalışma verileri toplanırken hem standardizasyonu sağlamak hem de hasta verilerini kayıt altına almak için daha öncesinden hazırlanan çalışma formu kullanıldı.

Acil Servis kabulünde tüm hastalara elektrokardiyografi (EKG) ve akciğer grafisi çekildi. Laboratuvar testlerinden; kan gazı bulguları (pH, PCO2, PO2, HCO3, laktat), WBC, CRP, PCT kaydedildi. Lökosit düzeyi hastanemiz sysmex XN1000 cihazı ile, CRP AU5800 ile, PCT düzeyi ise mikrobiyoloji eliza ünitesinde Cobas E 601 cihazı ile bakılmıştır. PCT düzeyleri Cobas E601 cihazında (Roche Diagnostik) Elecsys kullanılarak elektrokemiluminesans (ECLIA) yöntemle çalışıldı. Kitin önerileri; PCT düzeyi >0,1 ng/ml ise bakteriyel enfeksiyon, >0,5 ng/ml ise sepsis/septik şok riski, >2,0 ng/ml ise yüksek sepsis/septik şok riski doğrultusunda idi.

Hastalar Prokalsitonin düzeyine göre 4 gruba ayrıldı.

Grup 1: Çok olası olmayan (prokalsitonin<0,10 ng/mL)

Grup 2: Olası Olmayan (prokalsitonin 0,10-0,25 ng/mL)

Grup 3: Olası (prokalsitonin 0,25-0,50 ng/mL)

Grup 4: Çok Olası (prokalsitonin >0,50 ng/mL)

Alevlenme süresince acil Serviste hastalara verilen tedavilerden; bronkodilatörler, antikolinerjikler, sistemik steroid, antibiyotik, noninvaziv mekanik ventilasyon (NIMV) ve invaziv mekanik ventilasyon (IMV) not edildi. Hastaların sonlanım şekilleri (acil servisten taburculuk, servise yatış, yoğun bakıma yatış ve exitus) kaydedildi.

İstatiksel Analiz

Tüm veriler IBM SPSS Advanced Statistics 20.0 paket programı kullanılarak değerlendirilmiştir. Tanımlayıcı bulgular sayı ve yüzdeler ile ortalama ve standart hata olarak verilmiştir. Gruplar arası karşılaştırmalar ki- kare ve iki ortalama arasındaki farkın anlamlılık testi ile incelenmiştir. Ki- kare testi ve iki ortalama arasındaki farkın anlamlılık testi için p değeri 0.05'ten küçük olması anlamlı olarak kabul edildi. Gruplar arasındaki risk değerinin hesaplanması için rölatif risk ve %95 güven aralığı sunuldu. Kruskal Wallis testi, Mann Whitney U Testi ve Sperman Rho Korelasyon testi de çalışmamızda kullanılan istatistik yöntemleridir.

Bulgular

Çalışmamıza dahil edilen 100 hastanın %87'si erkek ve yaş ortalaması 70,4±10,5 yıl idi. Olguların %78'inde dispne, %30'unda ortopne, %16'sında göğüs ağrısı ve %7'sinde paroksismal nokturnal dispne mevcuttu. Hastaların %56'sında KOAH dışında başka bir kronik hastalık öyküsü yoktu. Hastaların %23'ü aktif sigara içiciyken; %66'sı geçmişte sigara içicisi olduğunu ve %11'i sigarayı hiç kullanmadığını belirtti. Sigara kullanımı ortalama 39,1±13,1 yıldı. Olguların %37'si nebülizatör ile tedavi aldığını, %37'si oksijen kondansatörü olduğunu, %96'sının kısa ve uzun etkili β2 agonist ve %40'nın mast hücre stabilizatörü kullandığı öğrenildi (Tablo 1).

Hastalar acil servise başvurularında; hastaların tümüne β2 agonist ve antikolinerjik (ipratropium bromür monohidrat) verildiği, %96'sına steroid tedavisi verildiği, %62'sine antibiyotik verildiği görüldü. Bunun yanı sıra; hastaların %30'una Non-invaziv mekanik ventilasyon (NIMV) ve %4'üne invaziv mekanik ventilasyon (IMV) uygulandı (Tablo 1).

PCT düzeyine göre 4 gruba ayrılan hastaların yaş ortalaması ve cinsiyet açısından benzer oldukları görüldü (sırasıyla p=0.984 ve p=0.973). Vital parametreler açısından anlamlı fark saptanmadı. Grup 4'teki olguların daha fazla NIMV

ihtiyacı duyduğu ve acil serviste NIMV tedavisi başlandığı görüldü (p<0.001); fakat, IMV ihtiyacı açısından tüm gruplar arasında anlamlı fark saptanmadı (p=0.069). Sonlanımları değerlendirildiğinde; grup 4'te bulunan olguların diğer gruplar ile karşılaştırıldığında; daha az taburculuk, daha çok servis ve yoğun bakım yatış oranlarına sahip olduğu anlamlı olarak görüldü (p<0.001) (Tablo 2).

Tablo 1 Olguların demografik ve klinik değerleri

Parametre		n (%) / Ortalama±SD
Yaş (yıl)		70,4±10,5
Cinsiyet (Erkek)		87 (87)
Vital Bulgular (Geliş)	Sistolik KB (mmHg)	142,2±25,7
	Diastolik KB (mmHg)	81,6±19,3
	Nabız (atım/dk)	92,8±20,7
	Saturasyon (%)	89,2±6,3
	Ateş (°C)	39,7±32,9
	Solunum Sayısı (/dk)	24,8±3,5
Kronik Hastalık Öyküsü	Hipertansiyon	25 (25)
	Diabetes Mellitüs	14 (14)
	Konjestif Kalp Yetmezliği	5 (5)
	Yok	56 (56)
Sigara Kullanımı	Aktif İçici	23 (23)
	Geçmişte kullanım öyküsü	66 (66)
	Hiç kullanmamış	11 (11)
Sigara kullanım süresi (yıl)		39,1±13,1
Başvuru Şikayetleri	Dispne	78 (78)
	Ortopne	30 (30)
	Göğüs ağrısı	16 (16)
	ProksismalNoktürnal Dispne	7 (7)
Kullandığı tedavi (sürekli)	Nebülizatör tedavisi	93 (93)
	Oksijen kondansatörü	37 (37)
	Kısa ve uzun etkili β2 agonist	96 (96)
	Mast hücre stabilizatörü	40 (40)
Acilde uygulanan tedavi	β2 Agonist	100 (100)
	Antikolinerjik	100 (100)
	Steroid	96 (96)
	Antibiyotik	62 (62)
	NIMV	30 (30)
	IMV	4 (4)
Laboratuvar Sonuçları (Başvuru Anı bakılan)	WBC	10,91±5,45
	CRP	50,3±64,8
	PCT	0,93±1,67
Acil Servis Sonlanımı	Taburcu	55 (55)
	Servis Yatışı	37 (37)
	YBÜ Yatışı	8 (8)

SD: Standart Sapma; KB: Kan Basıncı; NIMV: Non İnvaziv Mekanik Ventilasyon; IMV: İnvaziv Mekanik Ventilasyon; WBC: Lökosit (White Blood Cell); CPR: C Reaktif Protein; PCT: Prokalsitonin; YBÜ: Yoğun Bakım Ünitesi

PCT ve CRP düzeylerine göre verilen tedavi ve sonlanım değerlendirildiğinde; antibiyotik başlanan olgular ile başlanmayan olgular arasında CRP ve PCT ortanca değerleri arasında anlamlı fark olduğu tespit edildi (sırasıyla p=0.017 ve p<0.001). Steroid tedavisinin CRP ve PCT ortanca düzeyleri ile anlamlı bir ilişkisi yoktu. NIMV ve IVM uygulanan ve uygulanmayan olgular arasında CRP ortanca değeri açısından anlamlı fark bulunmazken; PCT ortanca düzeyleri hem NIMV hem de IVM alan olgularda anlamlı yüksekti (sırasıyla p<0.001 ve p<0.001). Taburculuktan-yoğun bakım ünitesine kadar, hasta kritikliği arttıkça, PCT'nin de anlamlı olarak yüksek olduğu görüldü (p<0.001). Fakat sonlanım ile CRP arasındaki bu ilişki anlamlı farklı değildi (Tablo 3).

Tartışma

Günümüzde, enfeksiyon hastalıklarında antibiyoterapi kararının verilmesi, hekimler açısından yaygın bir problem olarak karşımıza çıkmaktadır. Gereksiz antibiyotik kullanımı hem antibiyotik direncine neden olması hem antibiyotik yan etkilerinin ortaya çıkması hem de ülkelere getirdiği mali yük nedeniyle araştırmacıları, akılcı ve uygun antibiyotik kullanımını belirlemek için bilimsel araştırma yapmaya sevk etmiştir. KOAH alevlenmelerinin etiyolojisinde yer alan etkenlerin belirlenmesi hem gereksiz antibiyotik tedavisinin önüne geçilmesine hem de ortaya çıkması muhtemel antibiyotik direncini ve hasta maliyetlerini sınırlar. Bu nedenle biz de bu çalışmamızda enfeksiyon gösterge parametrelerinden birisi olan PCT'nin KOAH alevlenmelerinde erken tanı ve antibiyoterapiye başlanmasında yol gösterici olup olamayacağını araştırdık.

Enfeksiyon hastalıklarını erken tanınmada, direnç gelişmesini önlemede ve antibiyoterapi kararının doğru verilebilmesinde laboratuvar parametrelerinin kullanılması çok önemli yer tutmaktadır. Enfeksiyonlar hastalıklarında tedavi kararı, günümüzde klinisyenler açısından hala ciddi bir sorun teşkil etmektedir. Bu nedenle, bakteriyel enfeksiyonlara özgü belirteçlerin kullanılması, hastalığın tanı ve takibinde yararlı olmaktadır [13]. Literatürdeki çalışmalarda; KOAH alevlenmelerinde serum PCT ve CRP düzeylerinin birbiriyle ilişkili olduğu ve PCT düzeylerinin antimikrobiyal tedavi başlanmasında yol gösterici olarak kullanılabileceği ortaya konulmuştur [14, 15]. Tanrıverdi ve arkadaşları tarafından yapılan bir çalışmada; PCT değerlerinin KOAH alevlenmelerinin etiyolojisinin aydınlatılmasında CRP'den üstün olduğu gösterilmiştir [15]. Vanoverschelde ve arkadaşlarının yaptığı

Tablo 2. Olguların demografik ve klinik verilerinin gruplara göre dağılımının incelenmesi

Parametre		Grup 1 n (%)/ Ortalama±SD	Grup 2 n (%)/ Ortalama±SD	Grup 3 n (%)/ Ortalama±SD	Grup 4 n (%)/ Ortalama±SD	p
Yaş (yıl)		69,8±11	70,1±10,3	70,6±12,6	70,7±10,2	0.984*
Cinsiyet (Erkek)		12 (92,3)	21 (84)	10 (83,3)	44 (88)	0.973**
Vital Bulgular	Sistolik KB (mmHg)	125,1±20,9	143,7±30,3	149,5±24	144,1±23,4	0.086*
	Diastolik KB (mmHg)	63,5±22,1	81,3±21,1	83,4±11,9	86±16,6	0.005*
	Nabız (atım/dk)	97,3±17	97,8±16,6	81,5±19,5	91,8±22,8	0.105*
	Saturasyon (%)	91,5±4,8	89,1±7	88,5±6	88,7±6,3	0.312*
	Ateş (°C)	36,6±0,6	36,4±0,5	36,5±0,4	43±46,5	0.386*
	Solunum sayısı (/dk)	24,5±3,2	24±3,6	25,4±2,8	25,1±3,6	0.616*
Laboratuvar Değerleri	WBC (x10^3/mL)	10,99±5,84	10,78±4,67	11,13±3,99	10,9±6,11	0.771*
	CRP (mg/L)	40,7±39,4	61,7±86,4	29,8±42,6	52±62	0.390*
	Prokalsitonin (ng/mL)	0,07±0,02	0,17±0,04	0,37±0,06	1,68±2,12	<0.001*
Acil Servis Tedavisi	Beta 2 agonist	13 (100)	25 (100)	12 (100)	50 (100)	0.987
	Antikolinerjik	13 (100)	25 (100)	12 (100)	50 (100)	0.996
	Steroid	12 (92,3)	24 (96)	12 (100)	48 (96)	0.665*
	Antibiyotik	5 (38,5)	11 (44)	8 (66,7)	38 (76)	0.001*
	NIMV	-	3 (12)	1 (8,3)	26 (52)	<0.001*
	IMV	-	-	-	4 (8)	0.069*
Sonlanım	Taburcu	11 (84,6)	23 (92)	7 (58,3)	14 (28)	<0.001*
	Servise yatışı	2 (15,4)	2 (8)	5 (41,7)	28 (56)	
	YBÜ yatışı	-	-	-	8 (16)	

Kruskal Wallis testi **Ki-kare testi; KB: Kan Basıncı; NIMV: Non İnvaziv Mekanik Ventilasyon; IMV: İnvaziv Mekanik Ventilasyon; WBC: Lökosit (White Blood Cell); CPR: C Reaktif Protein; PCT: Prokalsitonin; YBÜ: Yoğun Bakım Ünitesi

Tablo 3. Olguların tedavi ve sonlanım kararlarının CRP ve PCT düzeyleri ile ilişkisi

Parametre		CRP (mg/dL) Ortanca (min-max)	p	PCT (ng/dL) Ortanca (min-max)	p
Steorid kullanımı	Evet	27,5 (1-407)	0,937*	0,48 (0,03-10)	0,679*
	Hayır	21,5 (4-132)		0,39 (0,08-0,9)	
Antibiyotik kullanımı	Evet	41,5 (1-407)	0,017*	0,6 (0,03-10)	<0,001*
	Hayır	13,5 (1-151)		0,2 (0,05-4)	
NIMV tedavisi	Evet	23 (1-334)	0,775*	0,8 (0,1-10)	<0,001*
	Hayır	28,5 (1-407)		0,27 (0,03-2)	
IMV tedavisi	Evet	17 (3-334)	0,819*	7,93 (4-10)	0,001*
	Hayır	28 (1-407)		0,41 (0,03-5,3)	
Sonlanım	Taburcu	27 (1-407)	0,582**	0,2 (0,03-0,9)	<0,001*
	Servise yatışı	42 (1-334)		0,7 (0,06-9,86)	
	YBÜ yatışı	19 (3-213)		4,1 (0,9-10)	
Sonlanımı belirleme	Taburcu-Servise yatışı	-	0,297*	-	<0,001*
	Taburcu-YBÜ yatışı	-	0,726*	-	<0,001*
	Servis-YBÜ yatışı	-	0,917*	-	<0,001*

*Mann-Whitney-U testi, **Kruskal Wallis Testi

başka bir çalışmada ise; CRP düzeyinin, akut KOAH alevlenme hastalarında antibiyotik başlamak için güçlü bir belirleyici olduğunu bildirilmiştir [16]. Çalışmamızda, PCT düzeyi ile antibakteriyel tedavi başlanması arasında anlamlı korelasyon saptanırken; CRP ile anlamlı bir korelasyon saptanmamıştır. Aynı zamanda; çalışmamızda, PCT ve CRP düzeyleri arasında pozitif korelasyon olmasına rağmen bu ilişki istatistiksek olarak anlamlı bulunmadı. Bunun durum için çalışmaya dahil edilen hasta sayısı neden olabilir. Çalışmamızda, değerlendirme sonrası hastanede yatan hastalar ile acilden taburcu edilen hastalar

arasında ve YBÜ'ye yatan hastalar ile diğer hastalar arasında CRP düzeyi açısından anlamlı farklılık yoktu. Bunun yanı sıra; PCT düzeyinin hastanede yatırılan olgularda ve yine YBÜ yatışı yapılan hastalarda istatistiksel anlamda diğer hastalardan yüksek olduğu görüldü. Çalışma sonuçlarımız, hastalık şiddeti ile PCT'nin ilişkili olduğu; buna karşılık, CRP düzeyinin hastalığın şiddetiyle ilişkili olmadığı saptandı. CRP'nin, KOAH 'ta oluşan kronik inflamasyona bağlı olarak yüksek olabileceğini düşünmekteyiz. Bununla birlikte, KOAH'a özgü değildir; pek çok enfektif, inflamatuar ve malign durumlarda yükselmektedir [17].

Pazarli ve arkadaşlarının çalışmasında; KOAH alevlenmesi olan hastalarda, serum PCT düzeylerinin anlamlı olarak yüksek olduğu; PCT düzeyleri ile PCO2 seviyeleri arasında anlamlı bir korelasyon olduğunu bildirilmiştir [18]. Daubin ve arkadaşlarının KOAH alevlenme tanısı ile YBÜ'de yatan hastalar ile yaptıkları çalışmada; PCT düzeyleri ile KOAH alevlenmesinin şiddeti ve NIMV kullanımı arasında anlamlı ilişki saptamışlardır [19]. Bu çalışmalar yanında literatürde, PCT'nin rehberliğinde antibiyotik kullanımının, antibiyotik kullanım süresini kısalttığını; ancak, mortalite üzerine bir etkisi olmadığını bildiren çalışmalarda mevcuttur [20,21]. Çalışmamız sonuçlarında, PCT düzeyi ile KOAH alevlenme şiddeti arasında anlamlı bir ilişki saptandı ve PCT düzeyi yüksek hastalarda, PCO2'düzeyin daha yüksek olduğu ve NIMV ihtiyacının fazla olduğu görüldü. Çalışmamız sonuçlarında da literatür çalışmalarının belirtiği gibi daha fazla non invaziv ventilasyon desteğine ihtiyaç duyduğu sonucuna varmıştır.

Yine sonuçlarımızda, hastaların %55'i acil servisten taburcu edilirken; %45'inin ise hospitalizasyon ihtiyacı mevcuttu. Hospitalize edilen hastaların %8'i ise YBÜ'ye yatırıldı. Acil servisten taburcu edilen hastalarda PCT ortalaması 0,2 ng/ml, servise yatırılan hastalarda PCT ortalaması 0,7 ng/ml ve YBÜ'ye yatırılan hastalarda PCT ortalaması 4,1 ng/ml bulundu. Çalışmamızda PCT düzeyleri ile hastaların sonlanımı arasında anlamlı bir ilişki mevcuttu. Çalışmamız sonuçları, literatür çalışmalarının elde ettiği sonuçlara benzer sonuçlar göstermiştir.

Stolz ve arkadaşlarının yaptıkları bir çalışmada; KOAH alevlenmelerinde PCT, CRP ve copeptinin biyobelirteç olarak kullanılabilirliği araştırılmıştır. Bu çalışmada, serum PCT seviyeleri 0,25ng/ml ve üzerinde olan hastaların %25,8'inin ve PCT seviyesi 0,25ng/ml 'den düşük olan hastaların %5,9'unun YBÜ'ye yatırıldığı; buna karşılık, PCT seviyesi 0,25ng/ml'nin altında olan hastalardan %27,2'sinin 24 saatten az bir sürede hastaneden taburcu edildiği saptanmıştır. Bu çalışma, KOAH alevlenmelerinde PCT'nin prognostik belirteç olarak kullanılabileceğini ilk kez göstermiştir [19]. Xu ve arkadaşlarının pnömoni tanısı alan KOAH hastalarında yaptığı çalışmada; PCT ile hastalık ciddiyeti arasında anlamlı bir ilişki olduğunu gösterilmiştir [20]. Çalışma sonuçlarımızda, hastaların %55'i acil servisten taburcu edilirken; %45'inin ise hastanede yatış ihtiyacı mevcuttu. Hastanede yatırılan hastaların %8'i ise YBÜ'ye yatırıldı. Acil servisten taburcu edilen hastalarda PCT ortalaması 0,2 ng/ml, servise yatırılan hastalarda PCT ortalaması 0,7 ng/ml ve YBÜ'ye yatırılan hastalarda PCT ortalaması 4,1 ng/ml bulundu. Çalışmamızda PCT düzeyleri ile hastaların sonlanımı arasında anlamlı bir ilişki mevcuttu.

Hoult ve arkadaşlarının yaptığı bir meta-analiz incelemesinde; lökosit sayısı yüksekliğinin akut KOAH alevlenmelerde, altta yatan etkenin bakteriyel nedenli bir enfeksiyon olup olmadığı ayrımını yapmada başarılı bir biyobelirteç olmadığını belirtmişlerdir [22]. Bizim çalışmamızda, lökosit düzeyi ile hastaların sonlanımı arasında anlamlı bir ilişki saptanmadı.

Çalışma Kısıtlılıkları

Çalışmamızın birkaç kısıtlılığı mevcuttur. Bunlardan biri; çalışmamızın tek merkezli olması ve çalışmaya dahil edilen hasta sayısının az olmasıdır. Bir diğeri ise; sonlanımları ve tedavileri, kendi isteği ile hastaneden ayrılma ya da sevk olma nedeniyle takip edilemeyen hastaların çalışmadan çıkarılması ve bu hastaların verilerinin çalışmamız verilerini ne şekilde etkileyeceğinin bilinmemesidir.

Sonuç

KOAH atak nedeniyle acil servise başvuran hastalarda, PCT'nin hastalığın şiddeti, antibiyotik başlama kararı, NIMV ve IMV tedavisine ve hastaların acil servisteki sonlanımına karar vermede önemli bir belirteç olduğu düşünüyoruz. Bununla birlikte; çalışmamızda, inflamasyon göstergelerinden olan CRP ve lökosit sayısının KOAH alevlenme ile acil servise başvuran hastalarda antibiyotik başlanması, mekanik solunum destek ihtiyacı ve sonlanımını öngörmede uygun bir biyobelirteç olmadığı; bu nedenle tedavi kararı verilirken PCT düzeylerinin dikkat edilmesi gerektiği görüşündeyiz.

Etik Onam

Etik kurul onayı 3. Basamak hastanemizin etik kurulundan alındı (Etik kurul 28/02/2019 tarih ve 7/7 nolu kararı ile).

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Research Article

Symptomatic and morphometric analysis of lumbosacral transitional vertebrae: assessments by age and gender

Lumbosakral geçiş vertebralarının semptomatik ve morfometrik analizi: yaş ve cinsiyete göre değerlendirmeler

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Abstract

Aim: Lumbosakral transitional vertebrae (LSTV) are anatomical variations where a vertebra exhibits characteristics of both lumbar and sacral vertebrae. This study aims to assess anatomical changes in LSTV patients by measuring intervertebral disc height (IVDh), vertebral foramen anteroposterior diameter (FVAPd), and intervertebral foramen height (FIVh), with consideration of age and gender differences.

Material and Methods: This retrospective study included 274 patients diagnosed with LSTV. All images were acquired with a 1.5T magnetic resonance imaging device and a 32-channel lumbar coil. The presence of LSTV, forming the morphological data, was identified from coronal and sagittal reformat images and was classified as either lumbarization or sacralization. Morphometric data (IVDh, FIVh and FVAPd) were acquired from axial, sagittal, and coronal planes using both soft tissue and bone window settings.

Results: The mean age of patient was 41.6±13.0 years, and most of them were female (55.8%). LSTV was predominantly lumbarization (96.4%), with sacralization in the remaining cases. The overall mean FVAPd was 11.2±2.4 mm, mean IVDh was 9.1±1.8 mm, and mean FIVh was 18.8±2.4 mm on the right and 19.1±2.4 mm on the left. IVDh levels were consistent across age groups, while FVAPd values were similar between genders. Patients aged 40 and under had higher FVAPd and FIVh levels, and male patients had higher IVDh and FIVh levels compared to females.

Conclusions: The morphometric characteristics of LSTV may vary according to age and gender. Considering these factors in accurately identifying the anatomical variations of LSTV may play a significant role in determining appropriate treatment and management strategies.

Keywords: lumbalisation, lumbar canal, lumbasacral transitional vertebra, sacralisation, sacral canal

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Öz

Amaç: Lumbosakral geçiş vertebraları (LSTV), bir omurun hem lumbal hem de sakral vertebra özelliklerini gösterdiği anatomik varyasyonlardır. Bu çalışma, LSTV'li hastalarda yaş ve cinsiyet farklılıklarını dikkate alarak, intervertebral disk yüksekliği (IVDh), vertebral foramenin anteroposterior çapı (FVAPd) ve intervertebral foramen yüksekliğini (FIVh) ölçerek anatomik değişiklikleri değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntemler: Bu retrospektif çalışmaya LSTV tanısı almış 274 hasta dahil edilmiştir. Tüm MR görüntüleri 1.5T manyetik rezonans görüntüleme cihazı ve 32 kanallı lumbar coil ile elde edilmiştir. Morfolojik veriler oluşturan LSTV'nin varlığı, koronal ve sagittal reformat görüntülerden tespit edilerek lumbalizasyon veya sakralizasyon olarak sınıflandırılmıştır. Morfometrik veriler (IVDh, FIVh ve FVAPd), hem yumuşak doku hem de kemik pencere ayarları kullanılarak aksiyal, sagittal ve koronal düzlemlerden elde edilmiştir.

Bulgular: Hastaların ortalama yaşı 41.6±13.0 yıl olup, çoğunluğu (%55.8) kadındı. LSTV vakalarının büyük çoğunluğu (%96.4) lumbalizasyon, geri kalan vakalar ise sakralizasyon şeklinde görülmüştür. Genel olarak ortalama FVAPd 11.2±2.4 mm, ortalama IVDh 9.1±1.8 mm, ortalama FIVh sağda 18.8±2.4 mm ve solda 19.1±2.4 mm olarak bulunmuştur. IVDh düzeyleri yaş grupları arasında tutarlılık gösterirken, FVAPd değerleri cinsiyet açısından benzerdi. 40 yaş ve altındaki hastalarda FVAPd ve FIVh düzeyleri daha yüksek, erkek hastalarda ise kadınlara kıyasla IVDh ve FIVh düzeyleri daha yüksek bulunmuştur.

Sonuç: LSTV'nin morfometrik özellikleri yaş ve cinsiyete göre farklılık gösterebilir. Bu faktörlerin dikkate alınarak LSTV'nin anatomik varyasyonlarının doğru bir şekilde tanımlanması, uygun tedavi ve yönetim stratejilerinin belirlenmesinde önemli bir rol oynayabilir.

Anahtar Kelimeler: lumbalizasyon, lomber kanal, lumbosakral geçiş vertebrası, sakralizasyon, sakral kanal

Introduction

Lumbosacral transitional vertebraes (LSTVs) are congenital anomalies of the spine, characterized by the sacralization of the lowest lumbar vertebra or the lumbarization of the highest sacral vertebra [1]. LSTVs can lead to nerve root inflammation, which may result in "sciatica" or radicular pain patterns [2]. Although LSTVs are more commonly observed in older age and males, the prevalence in the general population has been reported to range from 4% to 35% [3]. This variation underscores the importance of precise morphometric analysis and standardized diagnostic approaches to accurately identify and classify LSTVs.

LSTVs presents a range of variations, from partial or complete sacralization of the L5 vertebra to partial or complete lumbarization of the S1 vertebra [4]. When L5 is entirely fused with the sacrum, four lumbar vertebrae are present. Conversely, if S1 is fully separated from the sacrum, the spine contains six lumbar vertebrae, which leads to an increased lordotic curvature [5]. Transitional vertebrae can modify the spine's normal load distribution and movement patterns, potentially causing a range of symptoms from chronic low back pain to radiculopathy, depending on the degree and type of vertebral transition [6]. Morphometric measurements, including intervertebral disc height (IVDh), anteroposterior diameter of the vertebral foramen (FVAPd), and height of the intervertebral foramen (FIVh), offer valuable information about altered biomechanics, disc degeneration, and nerve compression [7, 8].

Due to the higher prevalence of LSTVs in older age and males, we assumed that morphometric measurements might differ by age and gender. Additionally, these measurements may vary between patients with pain and those without. Therefore, this study aimed to investigate the relationship morphometric measurements (IVDh, FVAPd, FIVh) derived from magnetic resonance imaging (MRI) of patients with transitional vertebral anomalies and their age, gender, and pain status.

Material and Methods

Following the principles set forth in the Declaration of Helsinki, this retrospective study was conducted at the Erzincan Binali Yıldırım University, Mengücek Gazi Training and Research Hospital, Radiodiagnostics Department between January 2022 and July 2022. The study received approval from the Binali Yıldırım University Clinical Research Ethics Committee (Approval Date: 30.03.2023, Number: 2023-07/4). The local ethics committee waived the requirement of informed consent due to the retrospective nature of the research.

Study population

A total of 1164 patients who visited the Radiodiagnostic Department and underwent MRI of the lumbosacral region during the aforementioned dates were retrospectively examined in this study. Due to the possibility of altered normal anatomy, patients with disk degeneration, those over 69 years old, those with scoliosis, spondylolisthesis, pelvic or spinal trauma, and those who had previously undergone lumbar surgery were not included in the study. After this exclusion process, 274 patients with LSTVs were enrolled in this study.

Patient files and electronic records were used to obtain demographic and clinical information, including age, gender, pain status, and MRI findings.

Acquisition and Processing of Images

MRI images were obtained using a 1.5T MRI device equipped with a 32-channel lumbar coil (Magnetom Aera, Siemens, Erlangen, Germany). The images were acquired with the patient in the supine position. Sagittal T2-weighted images (time of repetition [TR]: 4120 ms, time of echo [TE]: 104 ms, average: 2, field of view: 280 mm, slice thickness: 4 mm, voxel size: 0.9 × 0.9 × 4 mm), sagittal T1-weighted images (TR: 646 ms, TE: 9 ms, average: 2, field of view: 280 mm, slice thickness: 4 mm, voxel size: 0.9 × 0.9 × 4 mm), and axial T2-weighted images (TR: 5070 ms, TE: 88 ms, average: 1, field of view: 190 mm, slice thickness: 4 mm, voxel size: 0.7 × 0.7 × 4 mm) were obtained and processed in multiplanar reconstruction and volume rendering technique formats. Three-dimensional images in the axial, sagittal, and coronal planes were used to obtain morphometric and morphological data in both soft tissue and bone window settings.

All MRI images were re-evaluated by a radiologist with 10 years of experience. The images were transferred to a Picture Archiving and Communication System (Akgün PACS Viewer v7.5, Akgün Software, Ankara, Turkey) workstation for analysis and to perform measurements in standard digital imaging and medical formats.

Assessment of Images

The presence of LSTV, forming the morphological data, was identified from coronal and sagittal reformat images and was classified as either lumbarization or sacralization. Morphometric data (IVDh, FIVh and FVAPd) were acquired from axial, sagittal, and coronal planes using both soft tissue and bone window settings.

The measurement of the intervertebral disc space was conducted in the sagittal plane by measuring the distance between the upper and lower concave points of the L4-5 lumbar vertebral bodies, using the bone window setting. In the axial plane, FVAPd was measured at the widest distance at the relevant level using the bone window setting. At the L4-5 level, the height between the superior vertebral notch of the lower vertebra and the inferior vertebral notch of the upper vertebra was measured as the intervertebral foramen height using the bone window setting.

Statistical analysis

All of the data were analyzed with IBM SPSS Statistics for Windows 22.0 (IBM Corp., Armonk, NY, USA). The normality distribution of the numerical variables was evaluated with the Kolmogorov-Smirnov test. All numerical data showed a normal distribution and were reported as mean ± standard deviation (SD). Student's T-test was used for comparisons of numerical variables between two groups, while ANOVA (post hoc: Bonferroni test) was used for comparisons involving more than two groups. Categorical variables were given as numbers and percentages, and inter-group comparisons were conducted with the Chi-square and Fisher exact tests. Pearson correlation analyses were applied to evaluate the relationships between the numerical variables. Significance was accepted at $P < 0.05$ (*) for all of the statistical analyses.

Results

The patients included in the study had a man age of 41.6 ± 13.0 years (range: 12-64), and most of them were female (n = 153, 55.8%). There was no significant difference in the mean age between female and male patients (42.2 ± 13.1 vs. 41.8 ± 13.0, p = 0.386). LSTV appeared as lumbarization in 96.4% of the patients (n = 264), while in the remaining patients, it was in the form of sacralization (n = 10, 3.6%). Pain was present in 61.7% of the patients (n = 169). The distribution of age, gender, and pain were similar between the lumbarization and sacralization groups. The mean IVDh (9.5 ± 2.1 mm vs. 9.1 ± 1.7 mm, p = 0.541) and mean FVAPd (11.2 ± 2.8 mm vs. 11.2 ± 2.4 mm, p = 0.996) were not significantly different between the lumbarization and sacralization groups, while the mean FIVh values for both the right and left sides were higher in the lumbarization group compared to the sacralization group (18.8 ± 2.4 mm vs. 16.9 ± 1.6 mm, p = 0.004 for right FIVh; 19.2 ± 2.3 mm vs. 17.0 ± 2.4 mm, p = 0.011 for left FIVh). Their basic characteristics are shown in Table 1.

Table 1. Demographic and clinical characteristics of the patients.

Variables	All population n = 274	LSGV		p
		Sacralization n = 10	Lumbarization n = 264	
Age, years	41.6 ± 13.0	41.8 ± 15.5	41.6 ± 13.0	0.984
Gender, n (%)				
Female	153 (55.8)	5 (50.0)	148 (56.1)	0.705
Male	121 (44.2)	5 (50.0)	116 (43.9)	
Pain, n (%)				
No	105 (38.3)	4 (40.0)	101 (38.3)	0.999
Yes	169 (61.7)	6 (60.0)	163 (61.7)	
Morphometric findings				
IVDh, mm	9.1 ± 1.8	9.5 ± 2.1	9.1 ± 1.7	0.541
FVAPd, mm	11.2 ± 2.4	11.2 ± 2.8	11.2 ± 2.4	0.996
FIVh, mm				
Right	18.8 ± 2.4	16.9 ± 1.6	18.8 ± 2.4	0.004*
Left	19.1 ± 2.4	17.0 ± 2.4	19.2 ± 2.3	0.011*

Data are shown as mean ±SD or number and percentage (%). * indicates a statistically significant difference at p<0.05. Abbreviations: FIVh, height of the intervertebral foramen; FVAPd, anteroposterior diameter of the vertebral foramen; IVDh, height of the intervertebral disc.

The mean IVDh levels did not significantly differ across age groups. The mean FVAPd levels were higher in the 40 and under age group compared to the other age groups, but were lower in the 60-69 age group (≤ 40 years: 11.8 ± 2.4 mm vs. 40-59 years: 10.9 ± 2.2 mm vs. 60-69 years: 9.7 ± 2.2 mm, p < 0.001). Similarly, both right and left mean FIVh levels were higher in the 40 and under age group and lower in the 60-69 age group compared to the other age groups (≤ 40 years: 19.3 ± 2.1 mm vs. 40-59 years: 18.6 ± 2.3 mm vs. 60-69 years: 17.4 ± 2.2 mm, p < 0.001 for right FIVh; ≤ 40 years: 19.7 ± 2.2 mm vs. 40-59 years: 18.9 ± 2.4 mm vs. 60-69 years: 17.9 ± 2.3 mm, p < 0.001 for left FIVh) (Table 2).

The mean IVDh (9.7 ± 1.8 mm vs. 8.6 ± 1.5 mm, p < 0.001), mean right FIVh (19.1 ± 2.6 mm vs. 18.5 ± 2.2 mm, p = 0.001), and mean left FIVh levels (19.7 ± 2.6 mm vs. 18.6 ± 2.1 mm, p < 0.001) were higher in male patients compared to female patients, while mean FVAPd levels did not differ between genders (11.3 ± 2.5 mm vs. 11.2 ± 2.4 mm, p = 0.714). Patients with pain had a higher mean IVDh level compared to those without pain (9.3 ± 1.7 vs. 8.7 ± 1.8, p = 0.011), while the other morphometric measurements showed no significant differences between patients with and without pain (Table 2).

Age exhibited a negative correlation with FVAPd levels (r = -0.262, p < 0.001), right FIVh levels (r = -0.210, p < 0.001), and left FIVh levels (r = -0.209, p = 0.001). A positive correlation was found between IVDh levels and both right and left FIVh levels (r = 0.286, p < 0.001; r = 0.264, p < 0.001; respectively). No significant correlation was observed between FVAPd levels and the other morphometric data (Table 3).

Table 2. The relationship between morphometric data and demographic characteristics.

Variables	n	IVDh	p	FVAPd	p	Right FIVh	p	Left FIVh	p
Age, years									
≤ 40	123	9.0 ± 1.6	0.430	11.8 ± 2.4 [b,c]	<0.001*	19.3 ± 2.1 [b,c]	0.001*	19.7 ± 2.2 [b,c]	<0.001*
41-59	126	9.2 ± 1.8		10.9 ± 2.2 [a,c]		18.6 ± 2.3 [a,c]		18.9 ± 2.4 [a,c]	
60-69	25	8.8 ± 2.0		9.7 ± 2.2 [a,b]		17.4 ± 2.2 [a,b]		17.9 ± 2.3 [a,b]	
Gender									
Female	153	8.6 ± 1.5	<0.001*	11.3 ± 2.5	0.714	18.5 ± 2.2	0.003*	18.6 ± 2.1	<0.001*
Male	121	9.7 ± 1.8		11.2 ± 2.4		19.1 ± 2.6		19.7 ± 2.6	
Pain									
No	105	8.7 ± 1.8	0.011*	10.9 ± 2.5	0.097	18.6 ± 2.4	0.345	18.9 ± 2.3	0.200
Yes	169	9.3 ± 1.7		11.4 ± 2.3		18.9 ± 2.3		19.3 ± 2.4	

Data are shown as mean ±SD. n, sample size. * indicates a statistically significant difference at p<0.05. a vs. ≤ 40 years group, b vs. ≤ 41-59 years group, c vs. ≤ 60-69 years group. Abbreviations: FIVh, height of the intervertebral foramen; FVAPd, anteroposterior diameter of the vertebral foramen; IVDh, height of the intervertebral disc.

Table 3. The correlation between age and morphometric data.

Variables	Correlation	IVDh	FVAPd	Right FIVh	Left FIVh
Age	r	0.013	-0.262	-0.210	-0.209
	p	0.835	<0.001*	<0.001*	0.001*
IVDh	r	-	-0.054	0.286	0.264
	p	-	0.371	<0.001*	<0.001*
FVAPd	r	-	-	0.026	0.069
	p	-	-	0.667	0.256
Right FIVh	r	-	-	-	0.843
	p	-	-	-	<0.001*

* indicates a statistically significant difference at p<0.05. Abbreviations: FIVh, height of the intervertebral foramen; FVAPd, anteroposterior diameter of the vertebral foramen; IVDh, height of the intervertebral disc.

Discussion

In this study, we found that lumbarization group was more prevalent than sacralization group among LSTV patients, with significant differences in FIVh values between these groups. Age was negatively correlated with FVAPd and FIVh levels, while pain presence was associated with higher IVDh levels. Additionally, male patients exhibited higher IVDh and FIVh values compared to female patients. These findings highlight the morphological variations in LSTV based on age, gender, and pain, providing important insights into its clinical implications.

Despite being a frequently observed congenital anatomical variation in the lumbosacral region, the pathophysiology and biomechanical effects of LSTV are still not fully understood. Previous studies have reported that the prevalence of LSTV varies between 4% and 35% [3]. This variation could be attributed to evaluation and interpretation errors, differences in individual diagnostic and classification criteria, and factors that may cause confusion among the study group data in various research studies across different studies [9-12]. In addition to these factors, age and gender differences play a significant role in the prevalence and manifestation of LSTV [13]. Studies have indicated that the frequency of LSTV can vary according to age, with certain age groups potentially more susceptible to the symptomatic effects of this anatomical variant [14]. Moreover, gender differences may also influence the presentation and severity of symptoms associated with LSTV, as well as the structural characteristics of the vertebrae involved [15, 16].

Morphometric analysis, which involves precise measurements of anatomical structures such as intervertebral disc height, the anteroposterior diameter of the vertebral foramen, and the height of the intervertebral foramen, is crucial in diagnosing LSTV accurately [17, 18]. The integration of detailed morphometric analysis into the evaluation of LSTV not only aids in the correct classification of the anatomical variation but also enhances the understanding of its biomechanical consequences [18]. By incorporating age and gender considerations into morphometric analysis, clinicians can achieve a more personalized and accurate diagnosis, which is essential for developing appropriate treatment plans. This, in turn, can lead to better management of symptoms and improved outcomes for patients affected by this condition.

A previous study reported that the mean L4-5 IVDh measurements in the sagittal plane were 9.4±2.9 mm, with men showing higher values than female (10.0±2.9 mm vs. 8.6±2.7 mm) [17]. Studies have indicated that the mean L4-5 IVDh levels in young healthy adults are approximately 12 mm [19]. Our study found that IVDh measurements were consistent with the literature and were higher in men than in female. A sagittal diameter below 12 mm is regarded as pathological, with measurements under 10 mm being indicative of severe spinal stenosis [20]. Several factors can contribute to the narrowing of the vertebral canal's diameter, which can result in the spinal cord being compressed and the onset of a clinical condition with neurological symptoms.

The literature contains very few studies on spinal canal diameter in patients with LSTV. FVAPd measurements did not show any gender differences. However, there was a negative correlation between FVAPd measurements and age, with significantly lower levels observed in patients over 60 years old. A negative correlation between increasing age and spinal canal diameter has also been reported in a previous study [21]. Changes in the aging spine generally occur in the discs and facet joints, but the bony lumbar vertebrae also undergo significant changes, typically decreasing in height and widening, with the vertebral body increasingly wedging posteriorly at L4-L5 as aging occurs [22, 23].

Spinal nerves pass through the intervertebral foramina. As a result, the ratio between FIVh and the space occupied by the nerve roots within these foramina influences the probability of root compression [24]. The spinal nerves and vessels that exit

through the FIV are one of the potential sources of pain in the lumbosacral region [25]. In the presence of LSTV, the altered anatomy of the region requires careful consideration during any surgical procedures or interventions in this area. Studies have shown that LSTV is correlated with an increase in nerve root symptoms and a higher incidence of foraminal stenosis [26, 27]. FIVh levels showed a decrease with age, in line with the literature [28]. Also, FIVh levels were higher in males than in females [29].

This study had certain limitations. Firstly, the study was conducted at a single center. The patient population in the study might have been confined to a particular geographical region or clinical environment, potentially limiting the generalizability of the findings. Secondly, the study did not include healthy individuals without LSTV, which could complicate the determination of LSTV's specific effects. Controlled studies would provide clearer insights into the impact of LSTV on spinal biomechanics and symptomatology. Thirdly, while the study focused on specific morphometric parameters (IVDh, FIVh, FVAPd), it did not account for other potentially relevant factors, such as body mass index, physical activity levels, or comorbidities that might influence spinal morphology and LSTV's clinical presentation. Including these variables in future research could help identify additional factors that interact with LSTV to affect spinal health. Lastly, long-term follow-up data for the patients were not available. This might provide more meaningful insights into whether LSTV, which may be mild or asymptomatic in the early stages, eventually leads to more noticeable symptoms or how its effects on spinal biomechanics change over time.

Conclusions

LSTV are the most commonly encountered benign anatomical variations in the lumbosacral spine by spine surgeons. The biomechanical changes caused by LSTV can differ based on the patient's age and gender. Thus, morphometric analyses that consider factors such as age and gender are of critical importance in the diagnosis and treatment of LSTV. These analyses can play a key role in accurate diagnosis, symptom management, and the formulation of treatment plans, enabling the development of more personalized approaches tailored to the individual needs of patients.

Ethics Approval

The study was performed in accordance with the Declaration of Helsinki, and was approved by the Binali Yıldırım University Clinical Research Ethics Committee (Approval Date: 30.03.2023, Number: 2023-07/4).

Informed Consent

The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

Conflicts of Interest Statement

The authors declare they have no conflicts of interest.

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Availability of Data and Material

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

Author Contributions

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

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Research Article

The three years' experience of long and very long chain fatty acid analysis

Uzun ve çok uzun zincirli yağ asit analizinde üç yıllık deneyim

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Abstract

Aim: Cellular lipids, such as cholesterol esters, sphingolipids, and glycerolipids contain Fatty acids (FAs). FAs take place in many living structures and FAs are useable for diagnosing and examining some diseases. FAs including 22 or more carbon atoms are defined as very long-chain fatty acids (VLCFAs). This study aimed to evaluate Ankara Bilkent City Hospital's results of VLCFA analysis data and present contributions to the literature.

Material and Methods: The present study involved a total of 5973 C22:0, 5973 C24:0, 5973 C26:0, 5664 phytanic acid, and 5658 pristanic acid analysis results, and 5973 C24/C22 and, 5658 C26/C22 ratios. The VLCFA analysis was performed by the SHIMADZU Gas Chromatograph Mass Spectrometer (GCMS) QP2010 SE system with the Eureka and the Obikrom kits. The analysis results between 01/01/2020 and 31/12/2022 in Ankara Bilkent City Hospital Biochemistry Laboratory were involved.

Results: The positive results were as follows; 207 (%3.5) for C22:0, 149 (%2.5) for C24:0, 340 (%5.7) for C24:0/C22:0 ratio, 111 (%1.9) for C26:0, 158 (%2.9) for C26:0/C22:0 ratio, 89 (%1.6) for Phytanic Acid, and 8 (%0.1) for Pristanic Acid. The male group had a higher number of positive results for C22:0 ($p<0.019$) and C24:0/C22:0 ratio ($p<0.001$). The pediatric group had a higher number of positive results for C26:0/C22:0 ($p=0.032$).

Conclusion: We shared our three-year LCFA and VLCFA analysis experience with this study. We also evaluated the analysis results according to gender and age groups. The present study may be helpful for future investigations.

Keywords: Very Long Chain Fatty Acids; Gas Chromatography-Mass Spectrometry; Peroxisomal Disorders

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Öz

Amaç: Kolesterol esterleri, sfingolipidler ve gliserolipitler gibi hücresel lipitler, Yağ asitleri (YA) içerir. YA'lar birçok canlı yapıda yer almakta ve YA'lar bazı hastalıkların teşhisinde ve incelenmesinde kullanılmaktadır. 22 veya daha fazla karbon atomu içeren YA'lar çok uzun zincirli yağ asitleri (ÇUZYA'lar) olarak tanımlanır. Bu çalışmada Ankara Bilkent Şehir Hastanesi'nin ÇUZYA analiz verilerinin sonuçlarının değerlendirilmesi ve literatüre katkı sunulması amaçlandı.

Gereç ve Yöntemler: Bu çalışmaya toplam 5973 C22:0, 5973 C24:0, 5973 C26:0, 5664 fitanik asit ve 5658 pristanik asit analiz sonucu ile 5973 C24/C22 ve 5658 C26/C22 oranları dahil edildi. VLCFA analizi, Eureka ve Obikrom kitleri ile SHIMADZU Gaz Kromatograf Kütle Spektrometresi (GCMS) QP2010 SE sisteminde gerçekleştirildi. Ankara Bilkent Şehir Hastanesi Biyokimya Laboratuvarında 01/01/2020 ile 31/12/2022 tarihleri arasında yapılan analiz sonuçları dahil edildi.

Bulgular: Pozitif sonuçlar; C22:0 için 207 (%3.5), C24:0 için 149 (%2.5), C24:0/C22:0 oranı için 340 (%5.7), C26:0 için 111 (%1.9), 158 (%2.9) C26:0/C22:0 oranı için, Fitanik Asit için 89 (%1.6) ve Pristanik Asit için 8 (%0.1) idi. Erkek grupta C22:0 ($p<0,019$) ve C24:0/C22:0 oranı ($p<0,001$) açısından daha yüksek sayıda pozitif sonuç elde edildi. Pediatrik grupta C26:0/C22:0 için daha yüksek sayıda pozitif sonuç vardı ($p=0,032$).

Sonuç: Üç yıllık UZYA ve ÇUZYA analiz deneyimimizi bu çalışmayla paylaştık. Analiz sonuçlarını cinsiyet ve yaş gruplarına göre de değerlendirdik. Bu çalışma gelecekte yapılacak araştırmalara yardımcı olabilir.

Anahtar Kelimeler: Çok Uzun Zincirli Yağ Asitleri; Gaz Kromatografisi-Kütle Spektrometresi; Peroksizomal Bozukluklar

Introduction

Fatty acids (FAs) are a component of almost every cell [1]. FAs are the building blocks of fats [2]. Cellular lipids, such as cholesterol esters, sphingolipids, and glycerolipids contain FAs [3]. FA molecules are parts of membrane lipids, with varying numbers of double bonds, chain lengths, and hydroxylation positions [4]. The number of carbons in fatty acids varies between 2 and 34, and with the difference in carbon numbers, fatty acids can be classified according to the number of carbons they contain. Fatty acids with less than six carbon numbers are classified as short-chain fatty acids, fatty acids with six to ten carbon numbers are classified as medium-chain fatty acids, and fatty acids with more than ten carbon numbers are classified as long-chain fatty acids (LCFAs) [2]. FAs with 22 or more carbon atoms are very long-chain fatty acids (VLCFAs) [4]. Each VLCFA presents specific functions. They take part in the maintenance of myelin, formation of the skin barrier, spermatogenesis, anti-inflammation, retinal function, and liver homeostasis. VLCFAs do not independently obtain these functions [3]. VLCFAs can be synthesized from normal chain fatty acids by the elongation reaction in the endoplasmic reticulum. VLCFAs, which are activated by coenzyme A and become VLCFA-CoA, are transferred to the peroxisome. VLCFAs are shortened in the peroxisome and become ready for mitochondrial oxidation [5]. In mammals, VLCFAs are degraded by peroxisomal oxidation. With peroxisomal oxidation, the chain lengths of fatty acids are shortened and they become ready for mitochondrial beta-oxidation transfer [6]. Peroxisomal enzymes act on VLCFAs [7]. Being part of many living structures, from microscopic to macroscopic, makes fatty acids useable for diagnosing and examining some diseases [8]. In the human body, several diseases may occur due to impaired VLCFA metabolism [9]. X-linked adrenoleukodystrophy (X-ALD), childhood-onset cerebral adrenoleukodystrophy (CCALD), and adrenomyeloneuropathy (AMN) are some forms of related diseases [4].

In Ankara Bilkent City Hospital's medical biochemistry laboratory, FAs with 22 Carbon atoms (C22:0), with 24 Carbon atoms (C24:0), with 26 Carbon atoms (C26:0), and phytanic acid, and pristanic acid analyses are performed with the SHIMADZU Gas Chromatograph Mass Spectrometer (GCMS) QP2010 SE device. Furthermore, if requested by the clinicians C24/C22 and C26/C22 ratios are calculated and presented in the patient result reports. The purpose of this retrospective study, which includes LCFA and VLCFA analysis data conducted at Ankara Bilkent City Hospital between 01.01.2020 and 31.12.2022, is to contribute to the literature.

Material And Methods

A total of 5973 C22:0, 5973 C24:0, 5973 C26:0, 5664 phytanic acid, and 5658 pristanic acid analysis results, and 5973 C24:0/C22:0 and 5658 C26:0/C22:0 ratios were included in this study. LCFA and VLCFA analyses were performed by the SHIMADZU Gas Chromatograph Mass Spectrometer (GCMS) QP2010 SE system with the Eureka Fatty Acids in Plasma By GC/MS kit (Code GC75010) (Eureka S.R.L. Lab Division Direzione e

Coordinamento Sentinel CH. Spa) and the Obikrom VLCFA GCMS (KK.53/01.07.2021/Rev.00) (Obikrom Analysis and Laboratory Services Inc./Türkiye)

The Eureka Fatty Acids in Plasma By GC/MS kit (Code GC75010) (Eureka S.R.L. Lab Division Direzione E Coordinamento Sentinel Ch. Spa) contains three reagents, and these are Raegent A, Reagent B, and Reagent C. The procedure was as follows. 3ml of whole blood was taken to EDTA containing sample tube and centrifuged at 4000 rpm for 5 minutes. 100 µl plasma and 100 µl Reagent A were poured into a suitable glass tube and vortexed for 60 seconds and added 2ml of Acetonitril-HCL solution (The solution includes 8 ml acetonitrile + 2 ml 10M HCl) and vortexed for 60 seconds. Tubes were put at 110 °C for 46 minutes and during this time shaken every 15 minutes then cooled down at room temperature. 5 ml n-Hexane was added and vortexed for 60 seconds, 0,5 ml 10M HCl was added and vortexed for seconds, and centrifuged at 4000 rpm for 5 minutes. The supernatant was taken and transferred to a clean tube of 15 ml. 4 ml KOH solution (The solution was made up of 5,6 gr KOH+ 100ml ultrapure water.) was added, vortexed for 60 seconds, and centrifuged at 4000 rpm for 5 minutes. The supernatant was taken and transferred to a clean tube of 10ml and evaporated to dryness. After drying 50 µl Reagent B was added, vortexed for 60 seconds, and evaporated to dryness. After drying 50 µl M-BSTFA and 50 µl Reagent C were added, vortexed for 60 seconds, incubated at 65˚C for 35 minutes (min), cooled down to room temperature, and finally 1 l volume was injected into the GCMS system.

The Obikrom VLCFA GCMS kit (KK.53/01.07.2021/Rev.00) (Obikrom Analysis and Laboratory Services Inc./Türkiye) contains three reagents, Reagent A, Reagent B, and Reagent C. 100 µl plasma and 100 µl Reagent A were poured into a suitable glass tube and vortexed for 1 min and added 2ml of Acetonitril-HCL solution (The solution includes 4 ml acetonitrile and 1 ml 10M HCl.) and vortexed for 1 minute. Tubes were put at 110 °C for 46 minutes and during this time shaken every 15 minutes then cooled down at room temperature. 2ml of NaOH solution (The solution was made up of 2 gr NaOH, 1 ml distilled water, and 49 ml Methanol.) was added, vortexed for 1 minute, and incubated at 110 °C for 46 minutes and during this time vortexed every 15 minutes, cooled down to room temperature. 5 ml hexane was added to the tubes, and vortexed for 1 minute, 500 µl of 10M HCl was added, vortexed for 1 minute, and centrifuged at 4000 rpm for 5 minutes. After centrifugation, the upper phase is transferred to clean conical falcon tubes and 4 ml KOH solution is added to the tubes, vortexed for 1 minute, and centrifuged at 4000 rpm for 5 minutes. After centrifugation, the upper phase was discarded and the middle phase and lower phase were kept. 5 ml of hexane

was added to the tubes, and vortexed for 1 minute. 500 µl 10M HCl was, vortexed for 1 minute and centrifuged at 4000RPM for 5 minutes. After centrifugation, the upper phase was transferred to clean glass tubes. Samples were allowed to evaporate. After the evaporation process, 50 µl Reagent B was added, then vortexed for 1 minute, and evaporated. After the evaporation process 50ul MBSTFA and Reagent C were added, vortexed for 1 minute incubated at 65 ˚C for 35 minutes, and cooled down to room temperature. Finally, it was taken into an insert vial and injected into the GCMS device.

During the analysis, TRB 5MS 30mx0,25mmx1um column was used. The injection temperature was 280 ˚C, the split ratio was 10, Column Temperature was 120˚C x1 min and 20 ˚C/min up to 300 ˚C. The analysis was conducted in 38 minutes and the flow of the Helium gas was 1ml/min. MS temperature was 230 ˚C, interface temperature was 280 ˚C, the scan type was SIM, and the ions were as follows; pristanic IS (internal standard) 358.00, pristanic 355.00, phytanic IS 372.00, phytanic 369.00, C22 IS 401.00, C22 397.00, C24 IS 429.00, C24 425.00, C26 IS 457.00, C26 453.00.

Our hospital's laboratory information system includes disease diagnoses according to the International Disease Classification Codes. In the present retrospective study, the data of patients who underwent LCFA and VLCFA analysis in the Medical Biochemistry Laboratory of Ankara Bilkent City Hospital between 01/01/2020 and 31/12/2022 were evaluated by obtaining them from the hospital information system.

Our study involved a single result for each patient, and only the first result of patients who had fatty acid analysis multiple times was included. Ethics approval was acquired from Ankara Bilkent City Hospital's Ethic Committee for this study. (E1-23-3808). The researchers worked under the Declaration of Helsinki at every stage of the present study. In the present study, no informed consent was obtained from the patients.

Statistical Analysis

The data of descriptive statistics were enunciated as numerically, mean, median, and interquartile ranges (IQR), and categorical variables were enunciated as percentages. A chi-square test was used in the groups' categorical data comparison. A p-value <0.05 was accepted as statistically significant. IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA) was utilized for the Statistical analyses. Microsoft Excel 2021 was used for graphs.

Results

The present study involved a total of 5973 C22:0, 5973 C24:0, 5973 C26:0, 5664 phytanic acid, and 5658 pristanic acid analysis results, and 5973 C24/C22 and, 5658 C26/C22 ratios.

Each data was separately evaluated according to pediatric (0-18 years), adult (0-64 years), and geriatric (65 years and over) age groups and gender groups. The distribution of age groups is presented (Table 1).

The minimum analysis result values expressed to be considered as positive used in the analysis were the higher values of 90.3 µmol/L for C22:0, 79.4 µmol/L for C24:0, 1.3 µmol/L for C26:0, for 3.77 µmol/L Phytanic Acid, and1.5 µmol/L for Pristanic Acid. The minimum ratio values expressed as to be considered positive were the higher values of 1.008 for C24/C22 and 0.026 for C26/C22. LCFA and VLCFA test analysis data are presented (Table 2). LCFA and VLCFA test analysis data among genders (Table 3) and among age groups (Table 4) are presented. Percentages of Test Analysis Data Among Age Groups (Graph 1) and Test Analysis Data Among Genders (Graph 2) are presented.

Table 1. Distribution of Age Groups

	Pediatric Group	Adult Group	Geriatric Group	p*
C22:0 (µmol/L)	4 [3-9]	20 [19-41.5]	69.5 [65-74.5]	<.001
C24:0 (µmol/L)	4 [3-9]	20 [19-44]	67 [65-73.5]	<.001
C24:0/C22:0	4 [3-9]	20 [19-41.5]	69.5 [65-74.5]	<.001
C26:0 (µmol/L)	4 [3-9]	20 [19-41.5]	69.5 [65-74.5]	<.001
C26:0/C22:0	4 [2-9]	20 [19-42]	69.5 [65-74.5]	<.001
Phytanic Acid(µmol/L)	4 [3-9]	20 [19-21.75]	73 [68-None]	<.001
Pristanic Acid (µmol/L)	4 [3-9]	20 [19-21]	73 [68-None]	<.001

The data are presented with the median and interquartile ranges (IQR) of the groups.
p*: Kruskal Wallis Test

Table 2. Long and Very Long Chain Fatty Acid Test Analysis Data

	Negative N (%)	Positive N (%)
C22:0 (µmol/L)	5766 (96.5)	207 (3.5)
C24:0 (µmol/L)	5824 (97.5)	149 (2.5)
C24:0/C22:0	5633 (94.3)	340 (5.7)
C26:0 (µmol/L)	5862 (98.1)	111 (1.9)
C26:0/C22:0	5299 (97.1)	158 (2.9)
Phytanic Acid (µmol/L)	5575 (98.4)	89 (1.6)
Pristanic Acid (µmol/L)	5650 (99.9)	8 (0.1)

N: Number of the population

Table 3. Long and Very Long Chain Fatty Acid Test Analysis Data Among Genders

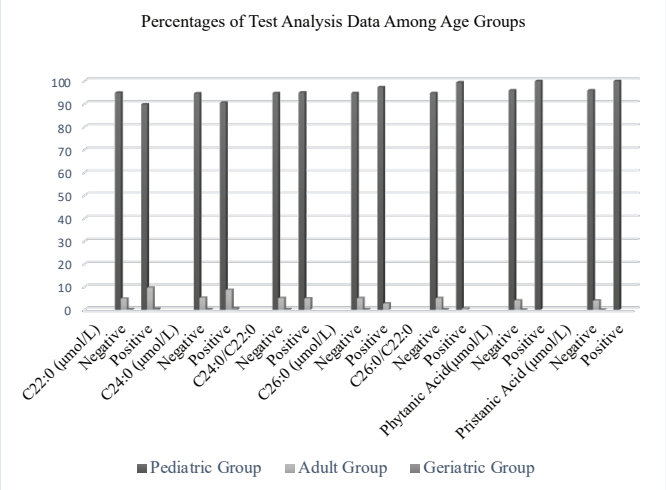
	Female	Male	
	N (%)	N (%)	p*
C22:0 (µmol/L)			
Negative	2342 (40.6)	3424 (59.4)	0.019
Positive	101 (48.8)	106 (52.2)	
C24:0 (µmol/L)			
Negative	2375 (40.8)	3449 (59.2)	0.238
Positive	68 (45.6)	81 (54.4)	
C24:0/C22:0			
Negative	2347 (41.7)	3286 (58.3)	<0.001
Positive	96 (38.2)	244 (71.8)	
C26:0 (µmol/L)			
Negative	2389 (40.8)	3473 (59.2)	0.098
Positive	54 (48.6)	57 (51.4)	
C26:0/C22:0			
Negative	2157 (40.7)	3142 (59.3)	0.219
Positive	72 (45.6)	86 (54.4)	
Phytanic Acid(µmol/L)			
Negative	2243 (40.2)	3332 (59.8)	0.587
Positive	33 (37.1)	56 (62.9)	
Pristanic Acid (µmol/L)			
Negative	2269 (40.2)	3381 (59.8)	0.722
Positive	4 (50)	4 (50)	

p*: Chi-square Test, N: Number of the population

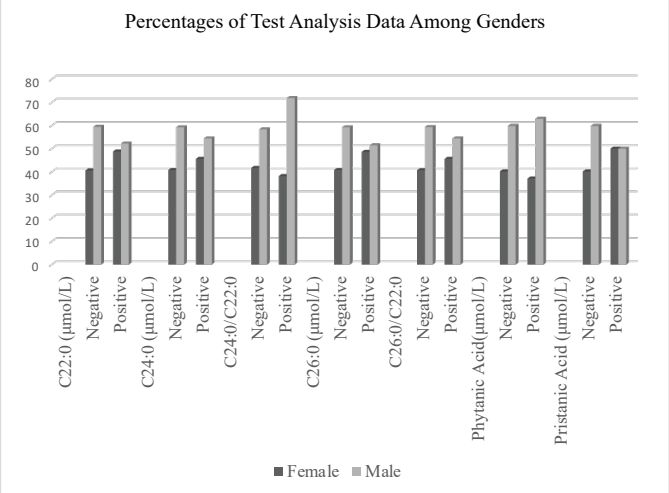
Table 4. Long and Very Long Chain Fatty Acid Test Analysis Data Among Age Groups

	Pediatric Group	Adult Group	Geriatric Group	
	N (%)	N (%)	N (%)	p*
C22:0 (µmol/L)				
Negative	5473 (94.9)	280 (4.9)	13 (0.2)	0.06
Positive	186 (89.9)	20 (9.7)	1 (0.5)	
C24:0 (µmol/L)				
Negative	5509 (94.6)	302 (5.2)	13 (0.2)	0.85
Positive	135 (90.6)	13 (8.7)	1 (0.7)	
C24:0/C22:0				
Negative	5336 (94.7)	283 (5.0)	14 (0.2)	0.654
Positive	323 (95)	17 (5)		
C26:0 (µmol/L)				
Negative	5551 (94.7)	297 (5.1)	14 (0.2)	0.46
Positive	108 (97.3)	3 (2.7)		
C26:0/C22:0				
Negative	5017 (94.7)	272 (5.1)	10 (0.2)	0.032
Positive	157 (99.4)	1 (0.6)		
Phytanic Acid(µmol/L)				
Negative	5344 (95.9)	228 (4.1)	3 (0.1)	0.146
Positive	89 (100)			
Pristanic Acid (µmol/L)				
Negative	5420 (95.9)	227 (4)	3 (0.1)	0.844
Positive	8 (100)			

p*: Chi-square Test, N: Number of the population



Graph 1: Percentages of Test Analysis Data Among Age Groups



Graph 2: Percentages of Test Analysis Data Among Genders

The diagnoses of patients whose results are evaluated as positive in the laboratory information system were as follows; certain infectious and parasitic diseases, neoplasms, diseases of the blood and blood-forming organs, and certain disorders involving the immune mechanism, endocrine, nutritional, and metabolic diseases, mental and behavioral disorders, diseases of the nervous system, diseases of the eye and adnexa, diseases of the circulatory system, diseases of the respiratory system, diseases of the digestive system, diseases of the skin and subcutaneous tissue, diseases of the skin and subcutaneous tissue, diseases of the musculoskeletal system and connective tissue, diseases of the genitourinary system, certain conditions originating in the perinatal period, congenital malformations, deformations and chromosomal abnormalities, symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified, factors influencing health status and contact with health services. As stated, the diagnoses of patients with positive analysis results varied.

Discussion

Plasma VLCFAs, C26:0/C22:0 ratio; phytanic and pristanic acids, and pristanic/phytanic acid ratio are some of the diagnostic tests in peroxisomal disorders [10]. Refsum disease, (both infantile and classic), Zellweger syndrome, Neonatal adrenoleukodystrophy, and Rhizomelic chondrodysplasia punctata are the common peroxisomal biogenesis disorders [11].

Elevated levels of plasma phytanic acid are essential for Refsum Disease [12]. In Refsum disease, plasma phytanic acid level is >200 µmol/L. This finding is pathognomic for Refsum disease [11]. In Zellweger syndrome, peroxisomal biogenesis is completely defective, and increased VLCFA, pristanic acid, and phytanic acid are observed in the plasma [12]. X-ALD which is the world's most common peroxisomal disorder is caused by mutations in the ABCD1 gene [13]. Peroxisomes's beta-oxidation impairment causes VLCFA accumulation in blood and some varied tissues [14]. Accumulated VLCFA values in the blood, high levels of C26:0, and high ratios of C24:0/C22:0 and C26:0/C22:0 are used for the diagnosis purposes of X-ALD. Rattay et al. examined the VLCFA results of 1908 patients in their study and stated that 45 cases were above the cut-off value. The X-ALD positivity of these patients was confirmed by ABCD1 gene mutation genetic testing. Of the 45 patients with high VLCFA values, 30 were found to be X-ALD positive and 15 were negative. [13]. In the present study, we evaluated a total of 5973 C22:0, 5973 C24:0, 5973 C26:0, 5664 phytanic acid, and 5658 pristanic acid analysis results, and 5973 C24/C22 and, 5658 C26/C22 ratios. The positive results were as follows; 207 (%3.5) for C22:0, 149 (%2.5) for C24:0, 340 (%5.7) for C24:0/C22:0 ratio, 111 (%1.9) for C26:0, 158 (%2.9) for C26:0/C22:0 ratio, 89 (%1.6) for Phytanic Acid, and 8 (%0.1) for Pristanic Acid (Table 2).

Abnormal lipid metabolism and abnormalities in peroxisome metabolism can be observed during the pathogenesis of osteoarthritis. Peroxisomal dysfunction may lead to the accumulation of VLCFAs and LCFAs in osteoarthritis patients [15].

Chu et al.; stated -in their study investigating the relationship between VLCFA and cancer- that decreased VLCFA levels were associated with slow growth of tumor cells and that VLCFA elongation was necessary for the growth of tumor cells [16].

Lipids also have functions in the nervous system. They play a role

in synapse stabilization, signal transmission and homeostatic balance of signaling molecules, protection of neurons and regulation of DNA, and inflammation responses. It has been stated that fatty acids may play a role in different stages of some retinal disease processes such as diabetic retinopathy, age-related macular degeneration, and retinitis pigmentosa. Very long-chain polyunsaturated fatty acids are depleted in diabetic retinopathy and age-related macular degeneration [17].

The patients we evaluated as positive in our study had diagnoses other than metabolic diseases that we obtained from the laboratory information system. Similar to our study, it has been reported in the literature that VLCFA levels are elevated in different kinds of diseases [15, 16, 17].

To the best of our knowledge, this is the first study presenting the LCFA and VLCFA analysis data of three years, comparing the groups according to gender and age, and evaluating the results by laboratory specialists. The data was sourced from one of Türkiye's largest laboratories, and fatty acid analyses are routinely conducted at our hospital.

The strength of our study is as follows: The data included in the present study covers 3 years; all data are evaluated in different age groups and genders. The limitations of our study are as follows: the data we obtained were evaluated only by laboratory experts and no clinical information nor genetic analysis results were involved, and we could not get information about the special diets, treatments, and medications of the people who underwent VLCFA and LCFA analyses, if any. It would be useful to conduct future studies that include detailed patient data.

Conclusion

We shared our three-year LCFA and VLCFA analysis experience with this study. We also evaluated the analysis results according to gender and age groups. We think the present study may be helpful for future investigations.

Conflict of interest

No person/organization financially supports the study and the authors have no conflict of interest.

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Research Article

Comparison of the effectiveness of LAFT technique and hybrid seton in the treatment of high-located anal fistula

Yüksek yerleşimli anal fistül tedavisinde LAFT tekniği ve hibrid setonun etkinliğinin karşılaştırılması

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Abstract

Aim: Many surgical techniques have been described for the treatment of high-located anal fistulas, and each surgical technique has its own advantages. In our study, we aimed to compare the long-term results of the hybrid seton technique and the laser ablation technique of the fistula tract in the surgical treatment of high-located anal fistulas.

Material and Methods: Patients who underwent laser ablation therapy (LAFT) and hybrid seton due to high-located anal fistula between June 2020 and April 2023 would be included in the study, and patients with a postoperative follow-up period of less than 6 months would be excluded from the study. The patients' files were evaluated retrospectively and their postoperative complications, preoperative and postoperative 1st month Cleveland fecal incontinence scores (CCFFSI scores), postoperative first day and first week visual analog scale (VAS) scores, follow-up periods, and recurrence rates were evaluated. Patients with a follow-up period of less than 6 months and patients treated for anal fistula due to Crohn's disease were excluded from the study.

Results: A total of 74 patients were evaluated. 32 patients were operated with LAFT (group 1), and 42 patients were operated with hybrid seton technique (Group 2). Postoperative anal abscess developed in 2 patients in Group 1 and in one patient in Group 2. Follow-up periods were calculated as 48.43±9.99, 39.26±11.17 weeks, respectively, and postoperative first day VAS scores were calculated as 4.53±1.36, 4.61±0.93, respectively. Postoperative Day 7 VAS scores were calculated as 0.96±1.14, 1.83±0.98, respectively. Preoperative CCFI scores were calculated as 1.71±1.25, 2.19±0.7, respectively. Postoperative CCFI scores were calculated as 1.78±1.23, 3.76±1.26, respectively. Postoperative recurrence occurred in 9 patients in group 1 and in 4 patients in group 2.

Conclusion: Although laser ablation of the fistula tract is a method that does not affect incontinence and has high postoperative comfort, its high recurrence rate should be taken into consideration.

Keywords: Hybrid seton, laser ablation of fistula tract, laser

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Öz

Amaç: Yüksek yerleşimli anal fistüllerin tedavisinde pek çok cerrahi teknik tanımlanmış her cerrahi tekniğin kendine ait avantajları vardır. Bizde çalışmamızda yüksek yerleşimli anal fistüllerin cerrahi tedavisinde hibrid seton tekniği ile fistül yolunun lazer ablasyonu tekniğinin uzun dönem sonuçlarını kıyaslamayı amaçladık.

Gereç ve Yöntemler: Haziran 2020- Nisan 2023 yılları arasındaki yüksek yerleşimli anal fistül nedeniyle lazer ablasyon tedavisi (LAFT) ve hibrid seton uygulanan hastalar çalışmaya dahil edilecek olup postoperatif takip süresi 6 aydan kısa olan hastalar çalışma dışı bırakılacaktır. Hastaların dosyaları retrospektif olarak değerlendirilerek hastaların postoperatif komplikasyonları, preop ve postop 1. ay Cleveland fekal inkontinans skorları(CCFFSI score), postop birinci gün birinci hafta visual analog scale (VAS) skorları, takip süreleri, nüks oranları değerlendirildi. Takip süreleri 6 aydan kısa olan hastalar, chrohn hastalığı nedeni ile anal fistül tedavisi uygulanan hastalar çalışma dışı bırakıldı.

Bulgular: Toplam 74 hasta değerlendirildi. 32 hasta LAFT (grup1), 42 hasta hibrid seton tekniği (Grup 2) ile opere edildi. Grup 1 de 2, Grup 2 de bir hastada postoperatif anal apse gelişti. Takip süreleri sırasıyla 48,43±9,99, 39,26±11,17 hafta; postoperatif birinci gün VAS skorları sırası ile 4,53±1,36, 4,61±0,93 olarak hesaplandı. Postop 7. Gün VAS skorları sırası ile 0,96±1,14, 1,83±0,98 olarak hesaplandı. Preop CCFI skorları sırası ile 1,71±1,25, 2,19±0,7 olarak hesaplandı. Postoperatif CCFI skorları sırası ile 1,78±1,23, 3,76±1,26 olarak hesaplandı. Postoperatif grup 1 de 9 grup 2 de 4 hastada nüks gelişti.

Sonuç: Fistül yolunun lazer ile ablasyonu inkontinansı etkilemeyen, postoperatif konforu yüksek bir yöntem olmasına rağmen nüks oranının yüksek olması göz önünde bulundurulmalıdır.

Anahtar kelimeler: hibrid seton, fistül traktının lazer ablasyonu, lazer

Introduction

Anal fistulas reduce the quality of life for patients due to pain and recurrent infections [1]. Anal fistula treatment aims to eliminate and heal the fistula tract, thus reducing symptoms and preventing recurrence [2]. There are many surgical treatments for anal fistula surgery. Hybrid seton (HS) and laser anal fistula tract ablation (LAFT) are some of these methods. Each method has its own advantages. In our study, we aimed to compare the HS and LAFT techniques in high-located anal fistulas.

Material and Methods

Patients who underwent laser ablation therapy (LAFT) and hybrid seton due to high-located anal fistula between June 2020 and April 2023 were included in the study, and patients with a postoperative follow-up period of less than 6 months were excluded from the study. The patients' files were evaluated retrospectively and their demographic data, postoperative complications, preoperative and postoperative 1st month Cleveland fecal incontinence scores (CCFFSI scores), postoperative first day and first week visual analog scale (VAS) scores, follow-up periods, relapse rates, and recovery times were evaluated. Patients with follow-up periods of less than 6 months, patients with Crohn's disease, cancer patients, patients who developed fistula secondary to trauma, patients who underwent anal fistula treatment due to recurrence, horseshoe and low-lying anal fistula were excluded from the study. Ethics committee approval of the study was obtained from a tertiary university hospital, and the Declaration of Helsinki designed the study.

Surgical Method

LAFT technique was applied in 2 sessions. If abscess was present in the first session, abscess drainage was performed. If there was no abscess, the fistula tract was revealed by MRI and mapping in accordance with Goodall's law, and loose seton was applied. In the second session, 4-6 weeks later, seton extraction was applied, the line was debrided and ablated with a laser probe (G.N.S neoLaser Ltd. © HaEshel, Israel) at the frequency settings as mentioned in the study [3]. The HS technique was applied in the lithotomy position, as mentioned in the study by Gulen et al. [4]. Figure 1 shows pictures of both surgical techniques applied. Patients were called for monthly check-ups in the first postoperative week, second week, and thereafter.

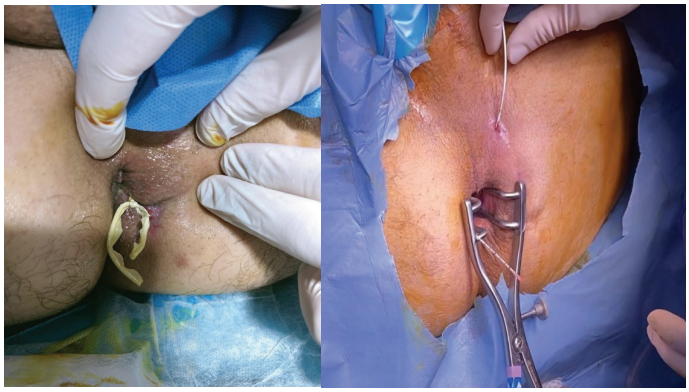

Figure 1. Applied version of LAFT and HS technique

Statistical analysis

For data evaluation, the SPPS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) statistical software was used. The variables were stated using the mean±standard deviation, percentage, and frequency values. Kolmogorov Smirnov test was performed to evaluate the homogeneity of the data. In the analysis of data, Mann-Whitney U test was used for the comparison of CCFFSI and VAS scores. Wilcoxon t-test was used to evaluate dependent groups. $P < 0.05$ was considered statistically significant.

Results

A total of 74 patients were evaluated. 32 patients were operated with LAFT (group 1), and 42 patients were operated with hybrid seton technique (group 2). In Group 1, 12 female and 20 male patients, and in Group 2, 10 female and 32 male patients were evaluated. The mean age of group 1 was calculated as 37.71±9.18, and the mean age of group 2 was 36.85±7.34 (p=0.98). In Group 1, 11 patients with intrasphinteric (IS), 2 extrasphinteric (EXS), 16 transsphinteric (TS), and 3 suprasphinteric (SS) fistulas were operated. In Group 2, 4 patients with EXS, 35 patients with TS, and 3 patients with SS fistulas were operated. The average follow-up period in Group 1 was calculated as 48.43±9.99 weeks, and in Group 2 the average follow-up period was calculated as 39.26±11.17 weeks (p=0.001). Recurrence was observed in 9 (28.1%) patients in Group 1 and 4 (9.5%) patients in Group 2 (p=0.03). Postoperative anal abscess developed in one patient in Group 1. Follow-up periods were calculated as 48.43±9.99, 39.26±11.17 weeks, respectively. Postoperative first day VAS scores were calculated as 4.53±1.36, 4.61±0.93, respectively (p:0.39). Postoperative day 7 VAS scores were calculated as 0.96±1.14, 1.83±0.98, respectively (p<0.001). Preoperative CCFI scores were calculated as 1.71±1.25, 2.19±0.7, respectively (p:0.07). Postoperative CCFI scores were calculated as 1.78±1.23, 3.76±1.26, respectively (p<0.001). The study analysis results are shown in table 1. When the preoperative and postoperative CCFSI scores were compared, the preoperative CCFSI value and postoperative CCFSI values in Group 1 were calculated as 1.71±1.25 and 1.78±1.23, respectively, and are shown in table 2(p=0.52). In Group 2, preoperative and postoperative CCFSI values were calculated as 2.19±0.7 and 3.76±1.26, respectively (p<0.001). Postoperative recurrence occurred in 9 patients in group 1 and in 4 patients in group 2.

Table 1. Analysis of study

	LAFT	Hybrid	p
Number of patient	32	42	
Gender	12 Female/ 20 Male	10 Female/ 32 male	
Age	37.71±9.18	36.85±7.34	0.98
Fistula type			
EXS	2(6.25%)	4(9.52%)	
IS	11(34.37%)	0	
TS	16(50%)	35(83,3%)	
SS	3(9.37%)	3(7,14%)	
Recurrence	9(28.1%)	4(9.5%)	0.03
Morbidity	5(15.6%)	2(4.8%)	0.22
ccfıpreop	1.71±1.25	2.19±0.7	0.07
Ccfıpostop	1.78±1.23	3,76±1,26	<0.001
Vas 1. day	4.53±1.36	4.61±0.93	0.39
Vas 7. day	0.96±1.14	1.83±0.98	<0.001
Healing time(week)	4.25±1.04	15.76±3.34	<0.001
follow-up time(week)	48.43±9.99	39.26±11.17	0.001

IS: Intrasphincteric EXS: Extrasphincteric TS: Transsphinteric SS: Suprasphinteric

Table 2. Comparison of preoperative and postoperative CCFSI values

	Preopccfı	PostopCcfı	p
LAFT	1.71±1.25	1.78±1.23	0.52
Hybrid	2.19±0.7	3.76±1.26	<0.001

Discussion

Although many sphincter-preserving techniques have been described for high-located anal fistulas, none of these techniques have taken the place in the literature as the gold standard treatment. In a prospective study on the LAFT technique, one of these techniques, the success rate was found to be 79% [5]. In another technique, the fibrin glue technique, the recurrence rate was found to be 36% [6]. The recurrence rate in the rectal mucosa advancement flap technique is stated to be 23%. In a study on another technique, endorectal mucosal advancement flaps, the recurrence rate was reported as 43% [7]. There are studies reporting recurrence rates in LAFT and hybrid seton techniques as 38% and 1.2%, respectively [8, 9]. Some of the factors affecting recurrence after anal fistula surgery have been stated as recurrent anal fistulas, diabetes, smoking, immunosuppressive diseases, and Crohn's disease [10]. Since our study was retrospective, the risk factors of the patients could not be evaluated. Although there is no study comparing the hybrid seton and LAFT technique in high-located anal fistulas, our study showed that the recurrence rate in the LAFT technique was higher than that of the hybrid seton.

Fecal incontinence poses a serious problem in high-located fistulas after anal fistula surgery. There are studies showing that there is no significant difference between preoperative and postoperative incontinence scores after hybrid seton surgery [9]. There are a few studies in the literature that evaluate incontinence using a scoring system after the LAFT technique. In the study conducted by Giamundo et al. [11], no significant difference was found between preoperative and postoperative CCFFSI scores after the LAFT technique. In our study, when the preoperative and postoperative CCFFSI scores were examined, it was seen that there was no significant difference between the preoperative CCFSI values in group 1 and the 1st month postoperative CCFSI values; In group 2, preoperative CCFSI scores were found to be significantly lower compared to the CCFFSI scores measured at the first postoperative month. Based on this, we can say that the LAFT technique is a more reliable technique in terms of incontinence compared to the hybrid seton technique.

Postoperative pain is an important factor in terms of patient comfort and quality of life after surgery in anorectal diseases. In a study conducted by Giamundo et al. [11] on the LAFT technique, the average VAS values in the VAS questionnaires they used to evaluate the preoperative and postoperative pain status were found to be 4 and no change was detected. In the study conducted by Ege et al. [9], post-operative day 1 and day 7 VAS scores were found to be 3.23 and 0.61, respectively. In this study, VAS values in Group 1 were found to be 4.53±1.36 and 0.8±1.02 on postoperative day 1 and postoperative day 7, respectively. In group 2, VAS values on postoperative day 1 and postoperative day 7 were calculated as 0.96±1.14 and 1.83±0.98, respectively, and postoperative day 7 VAS values in group 2 were higher than group 1. In the study, considering the VAS values at the first post-operative week, we can say that the LAFT technique is more comfortable than the hybrid seton technique in terms of pain. LAFT can be considered a comfortable method when evaluated in terms of postoperative pain. For more detailed postoperative comfort, quality of life surveys similar to page 36 are required. Howver, since our study was a retrospective study, patients could not be surveyed.

While the healing time in hybrid seton varies between 1 and 3 months [9], the average healing time in the LAFT technique is stated to be 5 weeks [12]. In our study, the healing time for hybrid seton was found to be 15.76±3.34 weeks, and for the LAFT technique, 4.25±1.04 weeks, and the healing time for hybrid seton was longer than that of the LAFT technique.

Conclusion

Although it is not a gold standard treatment for high-located anal fistulas, it is considered a preferable method in terms of preserving sphincter functions, postoperative pain comfort, and healing time. However, considering the surgical recurrence rates, it is higher than hybrid seton. We think that prospective studies comparing with other techniques are needed to access more detailed information.

Study limitations

The study is retrospective and the number of cases is low, which causes a limitation in the study.

Ethics

Informed Consent: All patients were informed about the procedure, and certificate of consent was taken for every patient.

Conflict of Interest statement

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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Research Article

The importance of adropin and hypoxia inducible factor-1 alpha in gastric cancer

Mide kanserinde adropin ve hipoksi ile indüklenebilir faktör -1 alfa'nın önemi

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Abstract

Aim: Gastric cancer accounts for 5.6% of all new cancer cases worldwide and is the fifth most common type of cancer. It ranks third in cancer-related mortality. With the current standard neoadjuvant treatment of localised gastric cancer, appropriate resection can be performed in approximately 75% of patients. While the two-year survival rate of patients is approximately 70 %, this rate decreases to 45 % in the fifth year. Although high curative treatment rates and long-term survival success are achieved with early diagnosis in many cancer types, unfortunately the same is not the case for gastric cancer and the unmet need for treatment continues. Adropin is a peptide secreted from many tissues in our body and has a regulatory role in energy homeostasis, angiogenesis, cell proliferation and cell migration processes. Hypoxia-inducible factor (HIF) is activated when oxygen levels decrease in tissues and regulates the growth, development, and differentiation of cells. A prospective study was planned to investigate the role of adropin and HIF-1α on the pathogenesis of gastric cancer and the relation of treatment response rates with adropin and HIF-1α levels by comparing adropin and HIF-1α levels in newly diagnosed locally advanced gastric cancer patients with adropin and HIF-1α levels in healthy individuals.

Material and Methods: Adropin and HIF-1α levels were compared between newly diagnosed patients with localised gastric cancer receiving neoadjuvant chemotherapy and healthy control group. We also examined whether there was a correlation between clinical and pathological response rates and adropin and HIF-1α levels in patients who completed the treatment.

Results: Adropin levels were statistically significantly lower and HIF-1α levels were statistically significantly higher in patients with gastric cancer. No significant difference was observed between adropin and HIF-1α levels and various clinical variables such as clinical response, pathological response, operability status, new pathological T (ypT) and new pathological N (ypN) stages..

Conclusion: It was important to demonstrate the relationship between adropin and gastric cancer, which had not been previously investigated and for which no data were identified through a literature review. It is obvious that adropin and HIF-1α are two important factors involved in gastric cancer. In addition adropin and HIF-1α may be two important parameters for early diagnosis of gastric cancer. Further studies are needed to elucidate the role of adropin and HIF-1α in gastric cancer.

Keywords: adropin, HIF-1α, gastric cancer

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Öz

Amaç: Mide kanseri tüm dünyada ki yeni kanser vakalarının %5,6'sını oluşturur ve beşinci en sık görülen kanser türüdür. Kansere bağlı ölüm sıralamasında ise üçüncü sırada yer almaktadır. Lokalileri mide kanserinde, günümüzde ki standart neoadjuvan tedavi ile hastaların yalaşık % 75'ine uygun rezeksiyon yapılabilmektedir. Hastaların iki yıllık hayatta kalma oranları yaklaşık %70 iken bu oran beşinci yılda %45'lere düşmektedir. Bir çok kanser türünde erken tanı ile yüksek küratif tedavi oranları ve uzun süreli sağkalım başarısı sağlanmasına rağmen mide kanseri için malesef aynı durum sözkonusu değildir ve karşılanmamış tedavi ihtiyacı devam etmektedir. Adropin, vücudumuzda birçok dokudan salgılanan; başlıca enerji homeostazisi, anjiyogenez, hücre proliferasyonu ve hücre göçü süreçlerinde düzenleyici rolü olan bir peptittir. Hipoksi ile indükenebilir faktör (HIF) ise dokularda oksijen seviyeleri düşünce aktive olur ve hücrelerin büyümesi, gelişmesi ve farklılaşmasını regüle eder. Yeni tanı almış lokal ileri mide kanseri hastalarında ki adropin ve HIF-1α sevyeleri ile sağlıklı bireylerdeki adropin ve HIF1-α seviyeleri karşılaştırılarak, adropinin ve HIF1-α'nın mide kanseri patogenezi üzerinde rolü ve tedavi yanıt oranlarının adropin ve HIF-1α seviyeleri ile ilişkisinin araştırılması amacıyla prosektif bir çalışma planlandı.

Gereç ve Yöntemler: Yeni tanı almış, neoadjuvan kemoterapi alacak olan lokalileri mide kanserli hastalar ve sağlıklı kontrol grubu arasında adropin ve HIF-1α düzeyleri karşılaştırıldı. Ayrıca tedaviyi tamamlayan hastalarda klinik ve patolojik yanıt oranları ile adropin ve HIF-1α düzeyleri arasında bir ilişki olup olmadığına bakıldı.

Bulgular: Adropin, mide kanserli hastalarda istatistiksel anlamlı olarak daha düşük, HIF-1α düzeyleri ise mide kanserli hastalarda istatistiksel anlamlı olarak daha yüksek bulundu. Adropin ve HIF-1α düzeyleri ile klinik yanıt, patolojik yanıt, operabilite durumu, yeni patolojik T (ypT) ve yeni patolojik N (ypN) evreleri gibi çeşitli klinik değişkenler arasında anlamlı bir farklılık görülmedi.

Sonuç: Daha önce araştırılmamış olan ve literatür taraması yoluyla herhangi bir veri tespit edilemeyen adropin ve mide kanseri arasındaki ilişkiyi ortaya koymak önemliydi. Adropin ve HIF-1α'nın mide kanserinde rol oynayan iki önemli faktör olduğu açıktır. Ayrıca adropin ve HIF-1α mide kanserinin erken teşhisi için iki önemli parametre olabilir. Adropin ve HIF-1α'nın mide kanserindeki rolünü aydınlatmak için daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: adropin, hıf-1α, mide kanseri

Introduction

Gastric cancer accounts for 5.6% of all new cancer cases worldwide and is the fifth most common type of cancer. It ranks third in cancer-related mortality (1). Gastric cancer varies in terms of gender and geographical distribution. It is particularly common in East Asia, Central-South America and Eastern Europe and is about twice as common in males as in females (1). In addition to advanced age, risk factors include genetic predisposition, diet, alcohol, smoking, and helicobacter pylori infection (2). Since there is no effective screening method for the early diagnosis of gastric cancer, more than two-thirds of patients are diagnosed at an advanced stage (3). A small proportion of patients are diagnosed at the local-local advanced disease stage. Local disease is defined as a tumour limited to the mucosa and submucosa and is treated by surgical resection. Locally advanced disease is defined as tumours between T2-T4a according to TNM staging system or tumours with lymph node infiltration (N+) (4). Locally advanced tumours are resectable tumours, but disease recurrence occurs in the majority of patients after surgery and five-year survival is between 10-15% (5). For this reason, the MAGIC study comparing surgery with preoperative epirubicin cisplatin 5-fluorouracil (EPC) chemotherapy was performed and it was shown that the results of preoperative chemotherapy were better (5). In the FLOT4 study, which compared EPC treatment before surgery with 4 cycles of dozataxel, oxaliplatin, 5-fluorouracil (FLOT) treatment before and after surgery, FLOT treatment improved pathological complete response (PCR), disease-free survival (DFS) and overall survival (OS) rates and is now considered the standard treatment (6). However, disease recurrence was observed in patients treated with FLOT before and after surgery and the mean survival was reported to be 50 months. In addition, pathological minimal response or non-response was observed in almost half of the patients after neoadjuvant treatment (6). In the view of this information, it is obvious that there are unknown factors such as histological type, genetic mutations, biochemical parameters that affect the character of the disease, prognosis, and chemotherapy response. Many guiding studies are needed to elucidate these factors.

Adropin is a peptide consisting of 76 amino acids discovered by Kumar et al. in 2008 (7). It is encoded by a gene called energy homeostasis associated gene (Enho) located on chromosome 9 and is expressed in many tissues in the human body (Figure 1). Adropin has been shown to stimulate angiogenesis, proliferation, and migration of endothelial cells via vascular endothelial growth factor receptor-2 (VEGFR2) (8). Adropin has also been suggested to increase endothelial nitric oxide (NO) levels via VEGFR2 and phosphatidylinositol 3-kinase-Akt (PIK3-AKT). NO improves endothelial cell functions, shows protective effect on endothelial cells and regulates angiogenesis (8). These findings suggest that adropin may be related to the regulation of angiogenesis in tumour cells, cell proliferation and migration, and response to treatment. A recent study showed that G-protein coupled receptor 19 (GPR19), an adropin receptor, is highly expressed in colorectal cancer (CRC) tissue. It was shown that adropin may play a role in regulating the energy homestasis of tumour tissue and in inflammatory-proinflammatory regulation by affecting macrophages in the tumour microenvironment. It has been reported that different tumour behaviour was observed at different levels of adropin (9). In a study investigating the correlation between adrenocortical carcinoma and adropin, it was shown that GPR19 was highly expressed in tumour tissue, exogenous adropin administration increased proliferation in tumour cells and was shown to be a poor prognostic factor for disease progression (10). Similarly, studies investigating the correlation of adropin with endometrial cancer (11), pancreatic ductal adenocarcinoma (12), and breast cancer (13) were also conducted and different results were obtained.

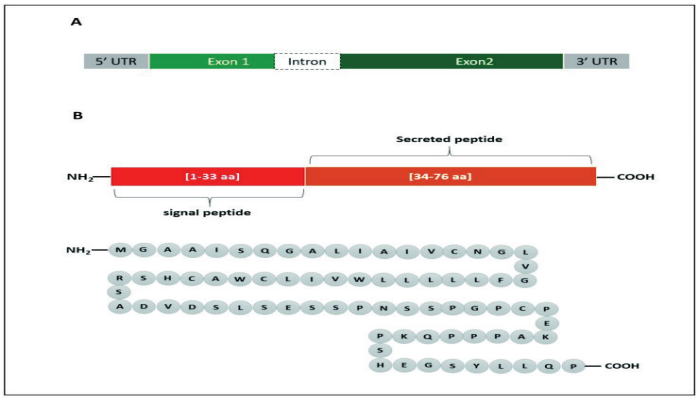

Figure 1: Structure of the Enho Gene and Adropin

Hypoxia-inducible factor (HIF) is a transcriptional factor involved in the regulation of oxygenation, an essential requirement for the growth, development, and differentiation of all living tissues. Ensuring oxygenation is also very important for tumour cells. It has been shown that HIF is activated in the tumour bed and different levels of HIF are associated with different tumour behaviours (14). HIF consists of two subunits, alpha and bata, and the alpha subunit is responsible for the regulation of oxygenisation (15). The alpha subunit is unstable when oxygen levels are high and is rapidly destroyed by pathways involving von Hippel-Lindau tumour suppressor protein (pVHL) (16). When the oxygen level decreases, the alpha subunit stabilises, dimerises with the beta subunit and activates the transcription of a series of genes. In studies conducted on this subject, it has been shown that HIF activation is related with tumour progression, regulation of vascularisation, cell proliferation, invasion and migration; it is also related with treatment resistance (17, 18) (Figure 2). In a recent study, HIF activation was shown to mediate the escape of cancer from the immune system (19). In the view of this information, many studies have been carried out in which some HIF inhibitors can be used in cancer treatment, but they have not been successful due to toxicity.

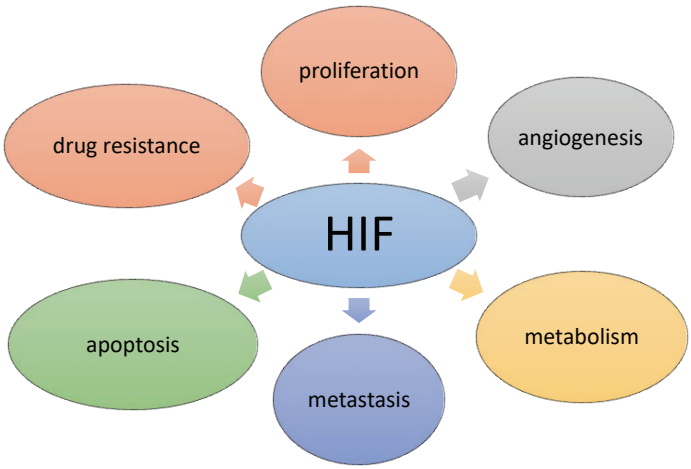

Figure 2: Processes Involved in Hif-1 Alpha in Gastric Cancer

Objective of the Study

There are many unknowns in the pathogenesis of gastric cancer and especially in response to treatment. By comparing adropin and HIF-1α levels in newly diagnosed locally advanced gastric cancer patients with adropin and HIF-1α levels in healthy individuals, we aimed to show whether adropin and HIF-1α have a role in the pathogenesis of gastric cancer and the correlation of clinical and pathological response rates after treatment with adropin and HIF-1α levels.

Material and Methods

A prospective study was planned by including newly diagnosed patients aged 18-80 years with locally advanced gastric cancer who applied to the Medical Oncology Clinic of Atatürk University Faculty of Medicine Hospital since October 2023 on a voluntary basis. Approval was obtained from Atatürk University Faculty of Medicine Clinical Research Ethics Committee. Our study was conducted in accordance with the rules of the World Medical Association (WMA) Declaration of Helsinki. Patients with type 2 diabetes mellitus, body mass index (BMI) <18 and >30, and Eastern Cooperative Oncology Group (ECOG) performance status 2 and above were excluded from the study. Age, gender, height, weight, ECOG performance score and presence or absence of chronic diseases were recorded at the time of initial diagnosis. Blood samples were taken from the volunteer control group (50 people) and patients eligible for the study (50 people) after fasting for 8 hours before treatment and centrifuged and stored at -80 degrees centrifugation. Adropin and HIF-1α were then analysed from the samples of 40 patients who completed the treatment process and whose information could be accessed. Adropin and HIF-1α kits were provided by the researchers. Positron emission tomography (PET-CT) results of the patients after treatment were then evaluated. According to Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1), complete response (score 1), partial response (score 2), stable disease (score 3) and progressive disease (score 4) were graded. In the operated patients, the tumour regression score was graded as pathological complete response (score 0), near complete response (score 1), partial response (score 2) and poor response or no response (score 3) according to the College of American Pathologists; 2017 protocol. Adropin and HIF-1α levels in the control and study groups were compared. In the study group, the correlation between adropin and HIF-1α levels and clinical and pathological response rates was examined. All analyses were performed using SPSS (SPSS version 25.0) statistical software package and $p < 0.05$ was accepted as statistical.

Results

SPSS 25.0 package programme was used for data analysis in the study. Descriptive data on the sociodemographic information of the participants are given as frequency tables (N and %). Data on continuous variables are given as median (IQR).

The data of the study were analysed in terms of normality assumptions Kolmogorov-Smirnov values ($p<0.05$). In this respect, Mann Whitney U test and Kruskall Wallis test, which are nonparametric tests, were performed to determine whether there is a significant difference between the groups with various variables. A P value less than 0.05 was considered statistically significant.

The data of forty locally advanced gastric cancer patients who were included in the study and whose information could be recorded completely until the last follow-up date were analysed. Among the patients, 27 (67.5%) were males and 13 (32.5%) were females. Mean age was 61.5 years and mean BMI was 26.1. The mean age and BMI were similar with the control group. After neoadjuvant chemotherapy, PET CT was performed and treatment response evaluation according to RECIST 1.1 criteria showed clinical complete response in 7 (17.5%) patients, partial response in 23 (67.5%) patients, stable disease in 6 (15%) patients and progression in 4 (10%) patients. A total of 25 (62.5%) patients underwent gastrectomy and d2 lymph node dissection, 22 of whom underwent R0 (negative surgical margin) and 3 underwent R1 (positive surgical margin) resection, and 15 (37.5%) patients were found unsuitable for surgery. In the operated patients, tumour regression score was checked according to the College of American Pathologists; 2017 protocol. 6 (25%) patients showed pathological complete or near complete response, 9 (37.5%) patients showed partial response and 9 (37.5%) patients showed non-response or poor response (Table 1).

Table 1. Distribution of various clinical and sociodemographic variables

Variables	Total (n=40)
Age, Mean±SD	61,5±7,2
BMI, Mean±SD	26,1±4,4
Gender, n (%)	
Male	27 (67,5)
Female	13 (32,5)
Clinical response, n (%)	
Complete response	7 (17,5)
Partial response	23 (67,5)
Stable disease	6 (15)
Progressive disease	4 (10
Pathological response, n (%)	
Complete and near complete	6 (25,0)
Partial response	9 (37,5)
No response	9 (37,5)
YpT, n (%)	
T1-T2	7 (29,2)
T3-T4	17 (70,8)
YpN, n (%)	
Lymph node Negative	9 (39,1)
Lymph node Positive	14 (60,9)
Resection, n (%)	
Operated	25 (62,5)
Non-operated	15 (37,5)

ypT: new pathological T stage, ypN: new pathological N stage

In the comparison of adropin and HIF-1α values between patients with gastric cancer and healthy control group, adropin values were found to be statistically significantly lower in patients with gastric cancer (p<0.001). HIF-1α levels were found to be significantly higher in patients with gastric cancer (p<0.001) (Table 2).

Table 2: Comparison of Adropin and HIF-1α Variables with Groups

	Group		
	Patient (n=30) Median (IQR)	Control (n=30) Median (IQR)	p
Adropin (pg/mL)	112,1 (55,1)	295,8 (217,2)	<0.001
HIF-1α (ng/ml)	14,9 (10,2)	1,10 (0,5)	<0.001

Mann Whitney U test, p<0.05 is statistically significant

Furthermore, no significant difference was found between adropin and HIF-1α levels and various clinical variables such as clinical response, pathological response, operability status, ypT and ypN stages (p>0.05) (Table 3).

Table 3: Comparison of Adropin and HIF-1α Variables with Various Clinical Variables

Variables	n	ANDROPIN Median (IQR)	p	HIF1-alpha Median (IQR)	p
Clinical response, n (%)					
Complete response	5	103,4 (75,3)	0.903[b]	19,6 (6,1)	0.721[b]
Partial response	18	122,4 (79,8)		9,8 (12,3)	
Stable disease	6	133,7 (120,1)		12,5 (13,1)	
Pathological response, n (%)					
Complete and near complete	4	127,2 (28,6)	0.699[b]	17,2 (13,6)	0.164[b]
Partial response	8	112,5 (104,2)		9,3 (7,1)	
No response	7	134,5 (104,7)		19,8 (14,2)	
YPT, n (%)					
Early stage	5	122,4 (101,5)	0.926[a]	14,7 (15,0)	0.405[a]
Advanced stage	14	122,2 (63,9)		16,3 (11,2)	
YPN, n (%)					
Negative	7	113,6 (35,1)	0.800[a]	14,6 (13,3)	0.837[a]
Positive	12	127,2 (91,2)		15,2 (11,1)	
Resection, n (%)					
Operated	19	122,4 (50,3)	0.102[a]	14,7 (11,7)	0.355[a]
Non-operated	11	98,8 (35,1)		15,1 (8,9)	

a: Mann Whitney U test, b: Kruskall Wallis test, p<0.05 is statistically significant

Discussion

Adropin is a peptide secreted from many tissues in our body and has a regulatory role in energy homeostasis, angiogenesis, cell proliferation and cell migration processes (8). In recent years, studies aiming to elucidate the correlation of adropin with various cancers have been conducted. As a result of the literature search, no study investigating the correlation of adropin with gastric cancer was found. Studies have shown that adropin levels change in preprandial-postprandial, obese individuals and patients with diabetes mellutus (20). In order to prevent these conditions from affecting the results, blood samples were taken in a fasting state, and subjects with a BMI >30 and diabetes mellitus were excluded from the study. The mean BMI was similar between the patient and control groups. The results of our study showed that adropin levels were significantly lower in patients with gastric cancer. In a study conducted in patients with endometrial cancer, similar to our study, adropin levels were found to be statistically significantly lower in patients with endometrial cancer compared to healthy individuals (11). It was also shown that adropin levels were lower in the tumour bed in patients with colon cancer, and the relation of adropin administration to these patients with disease progression was investigated. As a result of the study, it was reported that low dose adropin showed antitumour activity by increasing inflammatory activity (9). In our study, the correlation of adropin levels with disease progression, clinical-pathological treatment response and ypT-N stages was examined, but no significant difference was found.

Hypoxia-inducible factor (HIF) regulates the oxygenation of tissues by activating in case of hypoxia and is highly expressed for cancer cells to maintain their viability (21). In gastric cancer, HIF has been shown to increase tumour cell proliferation (22), inhibit apoptosis in tumour cells (23), cause drug resistance (24), increase angiogenesis (25), regulate energy homeostasis by promoting glycolysis (26) and cause tumour progression by these mechanisms. Based on these findings, many anti-cancer drugs targeting HIF in advanced gastric cancer have been tried (27). However, there is no anti-cancer therapy targeting HIF with an acceptable efficacy and side effect profile. In the literature review, the studies focused on patients with advanced gastric cancer and no study was found in patients with gastric cancer who were candidates for neoadjuvant treatment. In our study conducted in patients who were candidates for neoadjuvant treatment, HIF-1α levels were found to be statistically significantly higher than the control group in accordance with

the literature. In the literature, high HIF-1α levels have been shown to be associated with treatment resistance and poor prognosis. In our study, no significant correlation was found between HIF-1α levels and clinical-pathological treatment response, resection status and ypT-N stages.

In locally advanced gastric cancer, R0 resection cannot be performed in approximately 15% of patients with the current standard neoadjuvant treatment, and while the 2-year survival rate of patients is approximately 70%, this rate decreases to 45% in the 5th year (28). Although high curative treatment and long-term survival success is achieved with early diagnosis in many cancer types, unfortunately, the same is not the case for gastric cancer and the unmet need for treatment continues. It is obvious that adropin and HIF-1α are two important factors involved in this process. In addition, adropin and HIF-1α levels differ in patients with gastric cancer compared to the control group and based on this difference, adropin and HIF-1α may be two important parameters for early diagnosis of gastric cancer. Further studies are needed to elucidate the role of adropin and HIF-1α in gastric cancer.

Since our study was designed as a prospective study, the main limitations of our study are the long follow-up periods of the patients included in the study, the relatively small total number of patients due to the fact that some patients left the study and the information of some patients could not be accessed, and the planned number of subgroups could not be reached.

Conclusion

As a result of our study, adropin levels were statistically significantly lower and HIF-1α levels were statistically significantly higher in patients with gastric cancer. No significant difference was found between adropin and HIF-1α levels and various clinical variables such as clinical response, pathological response, operability status, ypT and ypN stages. It was important to demonstrate the relationship between adropin and gastric cancer, which had not been previously investigated and for which no data were identified through a literature review. As evidenced in the literature, HIF-1α has been demonstrated to be elevated in metastatic gastric cancer. This finding was also observed in the early stages of the disease. The present study did not find an association between adropin and HIF-1α and treatment resistance or prognosis. However, the number of patient subgroups was insufficient due to the prospective study design, long follow-up periods, and inability to reach patients who left the study. Further research is required to elucidate the relationship between adropin, HIF-1 alpha, and gastric cancer. This should be conducted with a larger number of patients and longer follow-up periods. It would also be beneficial to investigate the relationship between treatment resistance, recurrence rates, disease-free survival, and overall survival

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Research Article

Kolorektal kanserli hastaların demografik özellikleri

Demographic characteristics of patients with colorectal cancer

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Öz

Amaç: Kolorektal kanserler, kanserle ilgili mortalite ve morbiditenin en önemli sebeplerindendir. Tüm dünyada erkeklerde tanı alan en sık 3., kadınlarda ise en sık 2. kanserdir. Kolon kanseri erkek ve kadında hemen hemen eşit görülürken, rektal kanser erkeklerde K:E = 1:1.3 oranında daha sık görülür. Medyan tanı yaşı 70 olan kolorektal kanserler 50 yaş altında nadir görülür. Kolorektal tanısı ile takipli hastaların genel nitelikleri ve bu niteliklerin literatür ile uyumlu olup olmadığı araştırıldı.

Gereç ve Yöntemler: Çalışma, kesitsel, retrospektif kohort çalışması olarak tasarlandı. Temmuz 2011- Eylül 2015 tarihleri arasında Ankara Dışkapı Eğitim ve Araştırma Hastanesi Onkoloji Kliniği'nde takip edilen, kolonoskopi yapılarak tanısı konulan ve histopatolojik olarak tanısı doğrulanan kolorektal kanserli vakalar değerlendirildi.

Sonuç: Çalışmaya evre I-IV kolorektal kanserli 172 hasta alındı ve genel nitelikleri değerlendirildi. Hastalık literatür ile uyumlu şekilde erkek cinsiyette kadınlara göre daha sık tespit edildi Hastaların medyan yaşı 62 olarak saptandı. En genç hasta 27, en yaşlı hasta ise 89 yaşındaydı. KRK tanısıyla takip edilen erkek hastaların %37'sinde daha çok rektum kanserleri, %61'inde daha proksimal yerleşimli kolon kanserleri görülürken, kadınlarda %36 oranında rektum kanserleri ve buna yakın olarak %38 oranında daha proksimal yerleşimli kolon kanserleri görüldüğü saptanmıştır. Bu çalışmamız ile dünyada olduğu gibi ülkemizde de önemli morbidite ve mortalite nedenlerinden biri olan kolorektal kanserlerin demografik yapısını ve risk faktörlerini belirleyerek literatüre katkı sağlamayı amaçladık.

Anahtar Kelimeler: Kolorektal kanser, demografi, risk faktörleri

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Abstract

Aim: Colorectal cancers are one of the most important causes of cancer-related mortality and morbidity. It is the 3rd most common cancer diagnosed in men and the 2nd most common cancer diagnosed in women worldwide. While colon cancer is almost equally seen in men and women, rectal cancer is more common in men with a ratio of F:M = 1:1.3. Colorectal cancers are rare below the age of 50 years with a median age at diagnosis of 70 years. The aim was to investigate the general characteristics of patients diagnosed with colorectal cancer under follow-up, whether these characteristics are consistent with the literatüre or not.

Material and Methods: The study was designed as a cross-sectional, retrospective cohort study. Patients diagnosed with colorectal cancer, who were followed up at the Oncology Clinic of Ankara Dışkapı Training and Research Hospital and whose diagnosis was confirmed by colonoscopy and histopathological examination, were evaluated between July 2011 and September 2015.

Results: The study included 172 patients with stage I-IV colorectal cancer and their general characteristics were evaluated. The disease was found to be more common in the male sex than in the female sex in accordance with the literature. The median age of the patients was 62 years. The youngest patient was 27 years old and the oldest patient was 89 years old. It was found that 37% of male patients with CRC had rectal cancers and 61% had more proximal colon cancers, whereas 36% of female patients had rectal cancers and 38% had more proximal colon cancers. With this study, we have shown that colon cancers are a major cause of morbidity and mortality in our country as well as in the World

Keywords: Colorectal cancer, demographics, risk factors

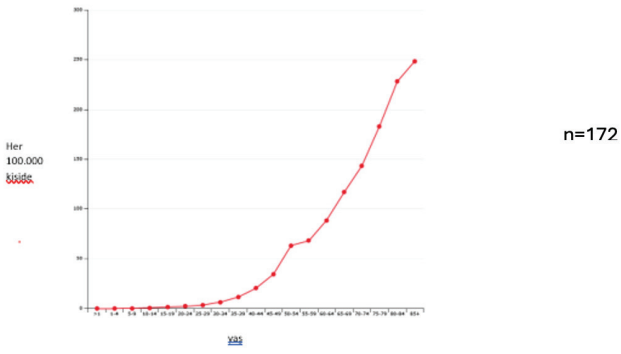
Giriş

Kolorektal kanserler (KRK) dünya çapında oldukça sık görülen ve ölüm oranları yüksek kanserlerdendir. Amerika Birleşik Devletleri (ABD), Kanada ve hemen tüm Avrupa ülkelerinde akciğer kanserinden sonra kanserden ölümlerin 2. sık nedenidir. Ancak erken evrede yakalandığında, minimal morbidite ve mortalitesi olan, uygun cerrahi girişim ile yüksek oranda küratif tedavi edilebilmektedir. Erken evrede tanısı konarak küratif cerrahisi yapılan hastalarda 5 yıllık sağ kalım oranları evre I tümörlerde %93, evre II tümörlerde %78, evre III tümörlerde %64 iken tanısı geç konan evre IV tümörlerde bu oran %8'e düşmektedir [1].

Dünya Sağlık Örgütü GLOBOCAN veri tabanına göre KRK, dünya çapında erkeklerde en sık üçüncü, kadınlarda ise ikinci en sık teşhis edilen kanserdir[2]. Hem insidans hem de mortalite oranları erkeklerde kadınlara göre önemli ölçüde daha yüksektir. Her yıl yaklaşık 153.000 yeni KRK vakası teşhis edilmekte olup bunların yaklaşık 107.000'i kolon kanseri ve 46.000'den fazla rektal kanser vakasıdır [3]. Ülkemiz verileri değerlendirildiğinde, 2018'de Sağlık Bakanlığı'nca yayınlanan kanser istatistik raporunda [4], kolorektal kanserler erkek ve kadınlarda en sık görülen 3.kanser çeşididir. Sıklığı erkeklerde yüz binde 24,8 iken kadınlarda yüz binde 14,7 olarak saptanmıştır ve bir yılda yaklaşık 18.750 kişiye kolorektal kanser teşhisi konulduğu belirtilmektedir.

Kolorektal kanserlerde başlıca risk faktörleri ileri yaş ve aile öyküsüdür. Hastaların %25'inde genetik yatkınlık olmaksızın aile öyküsü vardır. Diğer risk faktörleri ise diyet, vücut ağırlığı ve fiziksel inaktivite olarak sayılabilir. Olguların %2-4'ü Familyal Adenomatozis Poliposis (FAP) ve Herediter Non-Poliposis Kolorektal Kanser (HNPKK) olmak üzere genetik sendromlarla ilişkilidir. Yaş sporadik kolorektal kanser gelişimi için major bir risk faktörüdür. 40 yaşından önce kolorektal kanser gelişimi nadir iken, insidans 40-50 yaşlarından itibaren belirgin olarak artmaya başlar. Yaşa bağlı insidans oranları sonraki her 10 yılda belirgin artmaya devam eder (şekil 1) [5]. Değiştirilebilir yaşam tarzı özellikleri örneğin; sigara içmek [6], fiziksel inaktivite, sağlıksız diyet ve obezite de [7] yeni KRK gelişimi için gösterilmiş risk faktörleridir [8].

Bu çalışmada, KRK hastaların genel özellikleri ve bu özelliklerin literatür ile uyumlu olup olmadığı araştırılması amaçlanmıştır.



Şekil 1. Yaş- Kolorektal kanser gelişim ilişkisi

Gereç ve Yöntemler

Çalışma Dizaynı

Bu çalışma, Ankara Dışkapı Eğitim ve Araştırma Hastanesi etik kurulu onayı ile kesitsel, retrospektif kohort çalışması olarak tasarlandı ve 1964 Helsinki Bildirgesi ve daha sonra yapılan değişikliklerde belirtilen etik standartlara uygun olarak yapıldı. Temmuz 2011- Eylül 2015 tarihleri arasında Ankara Dışkapı Eğitim ve Araştırma Hastanesi Onkoloji kliniğinde takip edilen, kolonoskopi yapılarak tanısı konulan ve histopatolojik olarak tanısı doğrulanan kolorektal kanserli takipli hastalar çalışmaya dahil edildi. Bu amaçla hastaların dosyaları incelendi. Ayrıca hastalar aranarak veya kontrole geldiklerinde bilgileri alındı.

Ana Sonuçlar ve Diğer Değişkenler

Hastaların yaş ve cinsiyetleri belirlendi. Kolon, tümörün yerleşim yerini değerlendirmek için önce rektum, sigmoid, rektosigmoid, inen kolon, sol proksimal kolon, splenik fleksura, transvers kolon ve çekum olarak bölgelere ayrılarak sıklıkları belirlendi. Karşılaştırma çalışmaları yapmak için de bu bölgeler rektum ve kolon olarak 2 ana başlık altında toplandı. Yaklaşık 4 yıllık süre içinde kolon kanseri tanısı konulan hastaların, cinsiyetleri, tümörün yerleşim yeri, eşlik eden komorbiditeleri, sigara kullanımı, aile öyküsü, preoperatif CEA ve CA 19-9 düzeyleri, hastalık evresi, tümörün invazyon derecesi, tümörün histopatolojik tipi, perinöral, lenfovasküler invazyon varlığı, tümörün lokalizasyonu, preoperatif hemoglobin değerleri değerlendirildi.

İstatiksel Analiz

Veriler SPSS 22,0 programı ile istatistiksel değerlendirmeye alındı. Tanı tarihi olarak operasyon tarihi veya patolojik tanı tarihi kabul edildi. Hastalara ait bilgiler son kontrol tarihlerine veya ölüm tarihlerine kadar geçen süreyi kapsamaktadır. Tanımlayıcı istatistikler sürekli değişkenler için ortalama ± standart sapma veya ortanca (minimum-maksimum) olarak, nominal değişkenler ise hasta sayısı ve yüzde (%) olarak ifade edilmiştir. İstatiksel analizlerde tüm ölçümsel değişkenler için normalite testleri yapılmıştır. Karşılaştırma yapılan gruplar arasında ortalamalar yönünden farkın önemliliği Mann Whitney U testi, Anova ve Kruskal- Wallis analizleri ile değerlendirilmiştir. Nominal değişkenler Pearson'un Ki-Kare ve Fisher'in Ki-Kare testi ile değerlendirildi. Güven aralığı %95, istatistiksel anlamlılık için p değeri <0.05 kabul edilmiştir.

SONUÇLAR

Çalışmaya Ankara Dışkapı Eğitim ve Araştırma Hastanesi Onkoloji kliniğinde takip edilen, evre I-IV kolorektal kanserli 172 hasta alınmıştır. Değerlendirmeye alınan 172 hastanın medyan yaşı 62 olarak saptandı. En genç hasta 27, en yaşlı hasta ise 89 yaşındaydı. Ortalama yaş 62,5 ± 11,8 idi (tablo 1). Hastalık evresi ile tanı anındaki yaş arasındaki ilişki değerlendirildiğinde p=0.442 (p>0.05) saptandı ve yaş ile evre arasında istatiksel açıdan anlamlı bir ilişki olmadığı görüldü.

Tablo 1. Kolorektal kanserli hastaların demografik özellikleri

Yaş, yıl, meadian (min-max)	62 (27-89)
Cinsiyet, erkek, sayı (%)	98 (56.6)
Sigara kullanımı, sayı (%)	14 (40.1)
Komorbidite, sayı (%)	
Hipertansiyon	48 (28.4)
Diyabetes mellitus	38 (22.2)
Koroner arter hastalığı	22 (12.8)

Hastaların 98'i erkek (%56.6), 74'ü kadındı (%42.8). 69 hastanın (%40.1) özgeçmiş değerlendirmesinde sigara öyküsü olduğu saptandı. Soygeçmiş değerlendirilmesinde 43 hastanın (%25) hastanın ailesinde kolorektal kanser öyküsü saptanırken 129 hastada (%75) aile öyküsünün olmadığı tespit edildi. Hastalarda kolorektal kansere en sık eşlik eden hastalık hipertansiyon (%28.4) olarak saptandı. DM öyküsü % 22.2 ve koroner arter hastalığı öyküsü %12,8 olarak sıklıkla eşlik eden diğer hastalıklar olarak saptandı.

Tümör lokalizasyonuna göre kolorektal bölge anatomik olarak rektum, sigmoid, rektosigmoid, sağ kolon (inen kolon), sol proksimal kolon, splenik fleksura, transvers kolon ve çekum olarak bölgelere ayrıldı. Hastaların dağılımı incelendiğinde en sık tutulum rektumda saptandı (%23.4). Sigmoid kolon tutulumu %17,5, sağ kolon tutulumu %10,2 olarak kolon kanserinin sık görüldüğü diğer bölgeler olarak belirlendi (tablo 2).

Tablo 2. Tümör lokalizasyonuna göre dağılım

Tutulan bölge	Sayı (%)
Rektum	55 (23.4)
Sigmoid	41 (17.5)
Sağ (inen) kolon	29 (12.3)
Rektosigmoid	18 (7.7)
Transvers kolon	10 (4.2)
Çekum	8 (3.4)
Splenk fleksura	6 (2.6)
Sol proksimal kolon	5 (2.1)

Lenfovasküler invazyon olup olmadığı ile ilgili patoloji verisi 172 hastadan 148'inde mevcuttu. Verisi olan 148 hastanın %24'ünde invazyon saptanırken, %75'inde invazyon saptanmadığı görüldü. Perinöral invazyon bilgisi ise 149 hastanın patoloji raporunda belirtilmişti. Bu hastaların %14'ünde perinöral invazyon saptanırken, %85'inde invazyon saptanmadı.

Tümör invazyon dereceleri değerlendirildiğinde, hastaların 26'sında (%17.8) tümörün muskularis propiayı (T2), 78'inde (%53.4) serozayı (T3) bulundu, 34'ünde (%23,2) ise serozayı geçip serbest peritona boşluğu veya komşu organda tutulum (T4) gösterdiği tespit edildi. 26 hastanın patoloji raporunda tümör invazyon derecesi belirtilmemişti (tablo 3). Lenf nodu tutulumu ile ilgi bilgi edinilebilen 142 hasta vardı. Bunların 87'sinde (%61.2) lenf nodu tutulumu saptanmadığı (N0), 44'ünde (%30.9) <4 sayıda metastatik lenf nodu tutulumu olduğu (N1), 11'inde ise (%7.7) ≥4 sayıda metastatik lenf nodu (N2) tutulumu olduğu tespit edildi (tablo 3).

Tablo 3. Hastaların tümör invazyonu ve lenf nodu tutulum durumuna göre dağılımı

	Sayı (%)
Tümör invazyon derecesi	
T2	26 (17.8)
T3	78 (53.4)
T4	34 (23.2)
Lenf nodu tutulumu	
N0	87 (61.2)
N1	44 (30.9)
N2	11 (7.7)

TNM evrelemesi dosyasında belirtilmeyen 22 hasta mevcuttu. TNM evreleme sistemine göre evrelenen 150 hastanın 30'u (%17.3) evre I, 49'u (%28.3) evre II, 49'u (%28.3) evre III ve 23'ü (%13.3) evre IV olarak saptandı (tablo 4).

Tablo 4. Hastaların TNM evrelerine göre dağılımı

TNM Evresi	Sayı (%)
Evre 1	30 (17.3)
Evre 2	49 (28.3)
2A	37 (21.4)
2B	10 (5.8)
2C	2 (1.2)
Evre 3	49 (28.3)
3A	4 (2.3)
3B	42 (24.3)
3C	3 (1.7)
Evre 4	23 (13.3)
Evre belirtilmeyen	21 (12.7)

Hastalık evresi ve hastaların preoperatif CEA ve CA 19-9 düzeyleri arasındaki ilişikli değerlendirildi. Buna göre en yüksek CEA ve CA 19-9 düzeylerinin evre IV, en düşük düzeylerin ise evre I hastalıkta gözlendiği saptandı. Evreler arası CEA düzeylerinin karşılaştırıldığı non-parametrik testlerde evre I ve IV arasında p=0,00 (p<0.01), evre II ve IV arasında p=0,00 (p<0.01), evre III ve IV arasında p=0,001 (p<0.01) saptanarak istatiksel olarak anlamlı farklılık gözlemlendi (tablo 5). Evreler arası CA 19-9 düzeylerinin karşılaştırılmasında ise evre I ve IV arasında p=0,001 (p<0.01), evre II ve IV arasında p=0,006 (p<0.05) olarak saptandı ve istatiksel olarak anlamlı kabul edildi (tablo 6).

Tümör lokalizasyonu rektum ve kolon olarak 2 ana başlık altında toplandı. Hastaların preoperatif CEA ve CA 19-9 düzeyleri ile tümörün lokalizasyonu arasında ilişki olup olmadığı değerlendirildi. Kolon kanserli hastalarda preoperatif CA 19-9 düzeyi rektum kanserli olgulardan daha yüksek saptandı, p değeri= 0.03 (p<0.05), istatiksel olarak anlamlı bulundu. CEA düzeyleri ile tümör lokalizasyonu arasındaki ilişkinin değerlendirilmesinde ise p değeri= 0.28 (p>0.05) saptandı ve istatiksel olarak anlamlı kabul edilmedi.

Tartışma

Çalışmamızda kolorektal kanserli hastaların genel nitelikleri değerlendirildi. Hastalık literatür ile uyumlu şekilde erkek cinsiyette kadınlara göre daha sık tespit edildi [9]. Hastalarımızın median yaşı 62 saptanırken, tanı alan en genç hasta 27, en yaşlı hasta ise 89 yaşındaydı. Aile öyküsü hastaların çoğunda mevcut değildi. Hastalar tanı aldığında evre II (%28.3) ve evre III (%28.3) hastalığın daha sık olduğu gözlendi.

Literatürdeki birçok çalışmada kadınlarda görülen kolorektal kanserlerin daha proksimal yerleşimli olduğu belirtilmiştir [10]. Çalışmamızda KRK tanısıyla takip edilen erkek hastaların %37'sinde daha çok rektum kanserleri, %61'inde daha proksimal yerleşimli kolon kanserleri görülürken, kadınlarda %36 oranında rektum kanserleri ve buna yakın olarak %38 oranında daha proksimal yerleşimli kolon kanserleri görüldüğü saptanmıştır.

KRK gelişimindeki risk faktörleri; tarama önerilerini değiştirecek kadar yüksek riskli faktörler, önerileri değiştirebilir orta riskli faktörler ve tarama önerilerini değiştirmeyen düşük risk faktörleri olarak gruplandırılabilir (tablo 7). Sigara kullanımı tarama önerilerini değiştirmeyen düşük risk faktörleri arasındadır. Çalışmamıza katılan hastaların %40.1'inin sigara kullanım öyküsü var iken %59.8'inde sigara kullanımının olmadığı saptandı, ayrıca hastalık evresi ile sigara kullanımı arasında a istatiksel olarak anlamlı bir ilişki saptanmadı (p= 0.125). Aile öyküsünün KRK gelişimi için önemli bir risk faktörü olduğunu belirten çalışmalar mevcuttur [11, 12].

Çalışmamız değerlendirildiğinde 43 hastanın (%25) hastanın ailesinde kolorektal kanser öyküsü saptanırken 129 hastada (%75) aile öyküsünün olmadığı saptandı. Sonuçlarımız literatürdeki bu verilerden farklıydı.

KRK gelişimi için koruyucu faktörler de mevcuttur. Bunlardan bazıları; düzenli fiziksel aktivite, yüksek sebze meyve ve lif içeren beslenme, diyette yüksek folik asit alımı, B6, D vitamini ve kalsiyum desteği kullanımı, düzenli aspirin ve NSAİ kullanımı [13] ve postmenapozal hormon tedavileridir.

Tablo 5. Evreler arası preoperatif CEA düzeylerinin karşılaştırılması

Örnek1-Örnek2	Test İstatistiği	Standart Hata	Standart Test İstatistiği	Anlamlılık	Düzeltilmiş Anlamlılık
1,00-2,00	-.837	7,715	-.109	,914	1,000
1,00-3,00	-5,798	7,715	-.751	,452	1,000
1,00-4,00	-33,879	8,394	-4,036	,000	,000
2,00-3,00	-4,960	6,816	-.728	,467	1,000
2,00-4,00	-33,041	7,575	-4,362	,000	,000
3,00-4,00	-28,081	7,575	-3,707	,000	,001

Tablo 6. Evreler arası preoperatif CA 19-9 düzeylerinin karşılaştırılması

Örnek1-Örnek2	Test İstatistiği	Standart Hata	Standart Test İstatistiği	Anlamlılık	Düzeltilmiş Anlamlılık
1,00-2,00	-8,367	7,481	-1,118	,263	1,000
1,00-3,00	-17,403	7,709	-2.257	,024	,144
1,00-4,00	-33,100	8,482	-3,902	,000	,001
2,00-3,00	-9,036	6,591	-1,371	,170	1,000
2,00-4,00	-24,733	7,481	-3,306	,001	,006
3,00-4,00	-15,697	7,709	-2,036	,042	,250

Tablo 7. Kolorektal kanser risk faktörleri

Tarama önerilerini değiştirecek kadar yüksek risk faktörleri
Herediter krk sendromları Familyal adenomatoz polipozis Lynch sendromu (hnpcc) Adenomatoz polipler İnflamatuar bağırsak hastalıkları Abdominal radyasyon maruziyeti Kistik fibrozis
Tarama önerilerini değiştirebilecek orta risk faktörleri
Yaş ve Cinsiyet Akromegali Renal transplantasyon
Tarama önerilerini değiştirmeyen düşük risk faktörleri
Obezite Diyabetes Mellitus ve insülin direnci Kırmızı ve işlenmiş et tüketimi Sigara Alkol Kolesistektomi

Kolorektal kanser farklı şekillerde prezente olarak tanı alabilir. Hastalar şüpheli semptom ve/veya bulgular (hematokezya, melena, abdominal ağrı, açıklanamayan demir eksikliği ve/veya bağırsak alışkanlığında değişiklik vb.) ile başvurabildiği gibi, asemptomatik bireylerde rutin tarama sırasında veya intestinal obstrüksiyon, peritonit ya da gastrointestinal kanama gibi acil semptomlarla gelebilirler. Erken evre kolon kanserine sahip hastaların çoğu genellikle rutin tarama sırasında tanı alır. Kolorektal kanser taramalarının artması sayesinde asemptomatik evrede tanı konulma sıklığı artmıştır. Semptomlar genellikle tümörün lümen içinde veya bitişik yapılara doğru büyümesi sonucu ortaya çıkar. Bu yüzden semptomatik prezentasyon çoğunlukla ileri evre kolorektal kanseri düşündürür.

Hastalar metastatik hastalığa bağlı semptom ve bulgularla da prezente olabilir. Amerika Birleşik Devletleri'nde KRK hastalarının yaklaşık %20'sinde tanı anında uzak metastaz saptandığı belirtilmiştir [14]. Ayrıca lokal yayılımın da diğer etkenlerden bağımsız olarak sağ kalımı etkilediği bilinmektedir. T evrelemesi (TNM sistemi) değişken olmasına rağmen özellikle serozal tutulumun olup olmaması önem arz eder [15]. T1 ve T2 evre lezyonlarda sağ kalım %90 iken T3 lezyonlarda %80'dir [16]. Çalışmamıza katılan hastaların %17.8'inde tümör muskularis propriaya (T2), %53.4'ünde serozaya invaze (T3) olmuştu. %23,2'sinde ise tümör serozayı geçip serbest peritoneal boşlukta veya komşu organda tutulum (T4) gösteriyordu.

Bölgesel lenf nodu tutulumu cerrahi rezeksiyon sonrası sağ kalımı belirleyen en önemli faktörlerdendir. Nodal tutulum hem kolon hem de rektal kanserler de adjuvan tedavi için endikasyon oluşturur. Lenf nodu tutulumu, primer tümörün transmural invazyonu ve histolojik grade'i ile ilişkilidir [17]. Çalışmamızda hastalarımızın %61.2'sinde lenf nodu tutulumu saptanmadığı (N0), %30.9'unda <4 sayıda metastatik lenf nodu tutulumu olduğu (N1), %7.7'sinde ise ≥4 sayıda metastatik lenf nodu (N2) tutulumu olduğu tespit edilmişti.

Tümörün lenfatiklere, venöz veya küçük damarlara invazyonu da önemli bir prognostik faktördür. Amerikan Klinik Onkoloji Cemiyeti (ASCO) [18] ve Avrupa Medikal Onkoloji Cemiyeti (ESMO) [19], lenfovasküler invazyonu evre 2 kolon kanserinde yüksek risk kriterlerine dahil etmiştir. Değerlendirdiğimiz hastaların %24'ünde invazyon saptanırken, %75'inde invazyon saptanmadığı görüldü.

Birçok çalışmada perinöral invazyonun tek başına kötü prognozla ilişkili olduğu belirtilmiştir [20]. Prognostik önemi nedeniyle ASCO [18] ve ESMO [19] evre 2 yüksek risk kriterlerine dahil etmiştir. Hastalarımızın %14'ünde perinöral invazyon saptanırken, %85'inde invazyon saptanmadı.

Tümör evresinden bağımsız olarak preoperatif serum CEA seviyesinin prognostik önemi vardır. CEA seviyesinin >5ng/ml olması kötü prognoz düşündürür [20].

Literatür ile uyumlu şekilde çalışmamızda en yüksek CEA ve CA 19-9 düzeylerinin evre IV, en düşük düzeylerin ise evre I hastalıkta gözlendiği saptandı. Evre I ve IV arasında (p=0,00), evre II ve IV arasında (p=0,00) ve evre III ve IV arasında (p=0,001) CEA düzeylerinde, evre I ve IV (p=0,001) ve evre II ve IV (p=0,006) CA 19-9 düzeylerinde istatiksel olarak anlamlı farklılıklar gözlemlendi.

Çalışmamızın bazı sınırlılıkları mevcuttur. En önemli sınırlama çalışmanın kısıtlı hasta sayısı ile tek merkezde yapılmış olmasıdır. Bir diğer önemli sınırlılık çalışmamızın retrospektif olarak değerlendirilmiş olmasıdır. Daha fazla hasta sayısı ile birden çok merkezin katılımı ile yapılacak prospektif çalışmalar farklı sonuçlar verebilir.

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Çıkar çatışmaları

Yazarlar herhangi bir çıkar çatışması beyan etmemektedir.

Etik Kurul

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Research Article

Uncemented and cemented hemiarthroplasty for femoral neck fracture with end-stage renal failure

Son dönem böbrek yetmezliği olan femur boyun kırıklı hastalarda çimentolu ve çimentosuz parsiyel kalça protezi sonuçları

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Abstract

Aim: The aim of this study is to evaluate the results of hemiarthroplasty performed with cemented and uncemented femoral stem in femoral neck fractures with ESRF.

Material and Methods: Patients aged over 65 years with ESRF who admitted to our clinic for femoral neck fractures between January 2019 and June 2021 and underwent hemiarthroplasty, included in the study. Group 1 included patients with ESRF who underwent hemiarthroplasty with cemented stem due to femoral neck fracture. And group 2 included patients with ESRF who underwent hemiarthroplasty with uncemented stem due to femoral neck fracture. Functional scores of the patients and femoral stem loosening rates were evaluated with Harris Hip Score and radiographs.

Result: 48 patients (21 male, 27 female) were included in the study. Twenty of the patients were treated with posterior approach and 28 were treated with anterolateral approach. The mean age of the patients was 78,6±11,32 years (range: 65-93 years).The mean follow up time was 28,9 months (24-36 months).There was no significant difference between loosening of cemented and uncemented stems (p= 0,087). The mean HHS of the patients was 69.5 for group 1 and 71.8 for group 2 (range 40-85). There was no significant difference between HHS of group 1 and 2 (p>0.05).

Conclusion: Patients with ESRF who underwent hemiarthroplasty due to femoral neck fracture have a higher complication risk. The loosening rates and functional scores of cemented and uncemented hemiarthroplasty are similar.

Keywords: Renal failure, femoral neck fracture, hemiarthroplasty

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Öz

Amaç: Çalışmanın amacı son dönem böbrek yetmezliği (SDBY) olan femur boyun kırıklı hastalarda çimentolu ve çimentosuz parsiyel kalça protezi uygulamalarının sonuçlarını değerlendirmektir.

Gereç ve Yöntemler: Çalışmamıza SDBY olan ve hastanemize Ocak 2019 ve Haziran 2021 tarihleri arasında femur boyun kırığı nedeni ile başvuran 65 yaş üstü hastalar dahil edildi. Grup 1'e SDBY olan ve femur boyun kırığı nedeni çimentolu parsiyel kalça protez yapılan hastalar dahil edilirken, Grup 2'ye SDBY olan ve femur boyun kırığı nedeni ile çimentosuz parsiyel kalça protezi yapılan hastalar dahil edildi. Hastaların fonksiyonel skorları, femoral stem gevşeme oranları, Harris kalça Skorları (HSK) ve radyografileri değerlendirildi.

Bulgular: Çalışmaya 21 erkek, 27 kadın toplam 48 hasta dahil edildi. Hastaların 20'si posterior yaklaşım ile, 28'I ise anterolateral yaklaşım ile tedavi edildi. Hastaların ortalama yaşı 78,6±11,32 olarak belirlendi (aralık: 65-93 yaş). Ortalama takip süresi 28,9 aydı (24-36 ay). Çimentolu ve çimentosuz protezlerin gevşeme oranları arasında anlamlı bir fark izlenmedi (p=0,087). Grup 1 için ortalama HSK 69,5 iken, grup 2 için 71,8'di. HSK açısından iki grup arasında anlamlı bir fark yoktu.

Sonuç: SDBY olan ve parsiyel kalça protezi yapılan hastaların komplikasyon riskleri yükserktir. Yapılan çimentolu ve çimentosuz parsiyel kalça protezlerinn gevşeme oranları ve fonksiyonel sonuçları benzerdir.

Anahtar Kelimeler: Böbrek yetmezliği, femur boyun kırığı, parsiyel kalça protezi

Introduction

In patients with end-stage renal failure (ESRF), the incidence of femoral neck fracture is approxinately 4 times higher than general population (1,2). The treatment of femoral neck fractures complicated with ESRF continues to pose a great challenge for orthopedists.

Although there is a high risk of complications, surgical treatment is recommended for patients with femoral neck fracture with ESRF. (3-5). Because of the high risk of failure in internal fixation, arthroplasty is generally recommended. (6-8). Compared to the general population, mortality rates after femoral neck fractures for patients with ESRF is high , and perioperative complications are frequent. (9-11). However, there is no consensus on the methods those provide the best results of arthroplasty in patients with femoral neck fractures complicated with ESRF.

Uncemented or cemented femoral stems can be use for hemiarthroplasty. There is no consensus for femoral stem selection. The advantages of the cementing are cement interdigitation into bone and instant fixation (12-13). And osteointegration with pressfit implant is more difficult and limited in ESRF patients. Because the normal physiology of the bone is impaired in this patient group (14). However, there are studies reporting good results with the use of cementless stems in hemodialysis patients (15).

The aim of this study is to evaluate the results of hemiarthroplasty performed with cemented and uncemented femoral stem in femoral neck fractures with ESRF.

Material and Methods

Patients aged over 65 years with ESRF who admitted to our clinic for femoral neck fractures between January 2019 and June 2021 and underwent hemiarthroplasty, included in this retrospective study. Ethical approval was obtained before the study was conducted. (E1-21-2072). All researchers contributed to the study signed the final version of Helsinki's declaration.

Patients with femoral neck fractures, ESRF and minimum two years follow up were included the study. Patients whose data could not be accessed from the hospital record system, open fractures, multiple injuries, periprosthetic infections and pathological fractures were excluded from the study.

Group 1 included patients with ESRF who underwent hemiarthroplasty with cemented stem due to femoral neck fracture. And group 2 included patients with ESRF who underwent hemiarthroplasty with uncemented stem due to femoral neck fracture.

All of the patients received prophylactic antibiotic therapy (cefazolin sodium 1gr) before surgery. On the day before surgery, hemodialysis dependent patients underwent hemodialysis without heparinization. Patients underwent surgery using anterolateral or posterolateral approach. Cemented or uncemented femoral stem, 28 mm inner head and bipolar head were used for all patients. The case's senior surgeon decided which incision and stem to use. The cemented stems were performed with the first generation cementing technique. The suction drain was removed 24 hours after surgery. Sutures were removed on the 14th day after surgery. Low molecular weight heparin was used for 21 days. On the first day after the surgery, patients were mobilized with a walker. All patients were followed up at the 3, 6, 12, 24, 30 and 36 months after the surgery. Radiographs and Harris Hip Scores (HHS) of the patients were evaluated in every controls.

Patients age, gender, surgical approach, cement use, hemodialysis dependence, loosening and mortality were recorded from hospital record system. Aseptic loosening of the stem is defined as progressive radiolucency of more than 2 mm, progressive subsidence or migration of the implant (Figure 1). In addition, for cemented stems, cement mantle fracture indicated loosening.

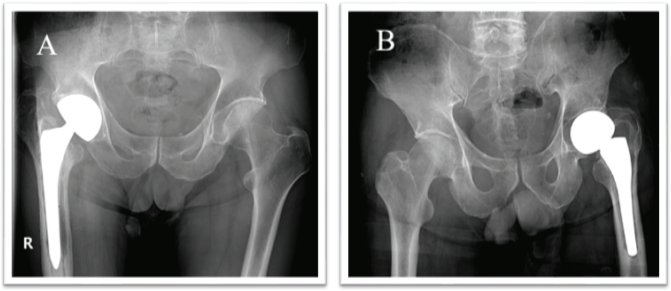

Figure 1. Cemented hip hemiarthroplasty with loosening (A), uncemented hip hemiarthroplasty with loosening (B)

Statistical analysis

For statistical analysis SPSS for Windows (SPSS Inc., Chicago, IL, USA) was used. Mann-Whitney U test was used to determine the relationships between parameters. The results were evaluated within 95% confidence intervals and $P < 0.05$ was considered significant.

Results

Seventy-eight patients with ESRF who underwent hemiarthroplasty due to femoral neck fracture were evaluated. Nineteen patients were excluded from the study because of death, 7 patients because of incomplete medical records and 4 patients because of septic loosening. So, 48 patients (21 male, 27 female) were included in the study. Twenty of the patients were treated with posterior approach and 28 were treated with anterolateral approach. The mean age of the patients was 78,6±11,32 years (range: 65-93 years).

In group 1, 23 patients (11 male, 12 female) treated with cemented stem (19 posterior, 4 anterolateral approach). The mean age of group 1 was 80,4±11,94 years (range 65-93 years). In group 2, 25 patients (10 male, 15 female) treated with uncemented stem (1 posterior, 24 anterolateral approach). The mean age of group 2 was 76,9±10,71 years (range 65-91 years).

The mean follow up time was 28,9 months (24-36 months). Stem loosening was detected in 7 patients (4 patients in group 1 and 3 patients in group 2). (Table 1) There was no significant difference between loosening of cemented and uncemented stems (p= 0,087). The mean HHS of the patients was 69.5 for group 1 and 71.8 for group 2 (range 40-85). There was no significant difference between HHS of group 1 and 2 (p>0.05).

Table 1. Stem loosening rates of the patients

Fixation type	Loosening	No loosening	Total
Cemented	4 (%17,39)	19 (%82,61)	23
Uncemented	3 (%12)	22 (%88)	25
Total	7 (%15,55)	41 (%74,45)	48

Discussion

In the current study, ESRF with femoral neck fractures, which is one of the challenging cases of orthopedics, were evaluated. No significant difference was observed in loosening rates and HHS in cemented and uncemented hemiarthroplasty.

Kaneko et al conducted a study to long bone fracture incidence and risk factors in patients with hemodialysis. They reported that the incidence of long bone fractures was high and the most common fracture was femoral neck fracture (59.8%). And revealed that there was a greater fracture risk with cardiovascular disease, female gender, older age, more years receiving dialysis, and diabetes (2). In this study, most of the patients were female and average age of the patients was 78,6±11,32 years.

In the light of current literature it could be said that, operative treatment is superior to conservative management for femoral neck fractures of patients with ESRF (3-5). However, higher complication and mortality rates were reported in surgical treatment of these patient group (3, 8, 16, 17). For our study, 19 patients were excluded from the study due to death and 4 patients due to septic loosening. Dislocation was observed in two of the patients who excluded from the study due to death and in one of the infected patients. In addition, superficial skin infection, arrhythmia and pulmonary thromboembolism were also observed in some patients. Stem loosening was detected for 7 of 48 patients in three years. Patients with ESRF who underwent arthroplasty due to femoral neck fracture have a higher risk of revision surgery.

The risk of revision surgery is high in the treatment of patients with ESRF and femoral neck fracture with internal fixation. (6, 7). Several authors have recommended arthroplasty because of lower complication rates compared to the treatment with internal fixation (8, 18). In the current study, all patients were treated with arthroplasty.

Another controversial issue in the treatment of ESRF patient group is whether cemented or uncemented arthroplasty is performed. Some authors recommend cemented, others uncemented arthroplasty (12, 14, 20). However, some authors concluded that for femoral neck fractures with ESRF, there is no difference in the loosening rates between uncemented and cemented hemiarthroplasty (16, 19). In the current study, there was no significant difference between loosening of cemented and uncemented stems.

There are some limitations for the current study. Firstly, our study has a retrospective design. Secondly, we have a small patient group. Thirdly, the surgeries were performed with different approachs (posterior and anterolateral). In the future, there is a need for a prospective, multicenter, large-scale study.

Conclusion

Patients with ESRF who underwent hemiarthroplasty due to femoral neck fracture have a higher complication risk. The loosening rates and functional scores of cemented and uncemented hemiarthroplasty are similar.

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Research Article

Validation study of Hba1c kit to be used in diabetic population

Diyabetik nüfus taramasinda kullanilacak Hba1c kiti doğrulama çalişmasi

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Abstract

Aim: A validation study of the HbA1c kit to be used in screening patients diagnosed with Diabetes Mellitus admitted to the hospital.

Material and Methods: In addition to the internal and external controls of the HbA1c kit used in routine analyses, in-laboratory verification and validation studies, validation steps of the test, accuracy (precision), and report range were carried out.

Result: All steps of the verification and validation of the HbA1c kit have been carried out and recorded in the hospital medical laboratory. Inter-study reproducibility (%CV) 0.88, Method / reference material comparison (% Bias) 3.94 Target: (% Bias + 1.65 (%CV) < TEa) As a result, TAH: 5.40 < TEa: 18 (rilibak) was calculated and The kit has been verified.The accuracy of the kit to be used in diabetic population screening is important as it will affect the clinician's prediction in the treatment and follow-up of a costly and common disease. All laboratories, whether commercial kit or not, should carry out verification procedures in order to increase laboratory reliability and quality. It should be mandatory to provide the right direction to clinicians, especially in the analysis of diseases that will affect society. Adding the validation data of the kit to the research data, which will be used in long-term studies that will affect a large population, will also increase the effectiveness of the study.

Keywords: Validation; Verification; Measurement Uncertainty; Truth; Precision; Diabetes Mellitus; HbA1c

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Öz

Amaç: Hastaneye başvuran Diyabetes Mellitüs tanılı hastalarda taramada kullanılacak olan HbA1c kiti doğrulama çalışması

Gereç ve Yöntemler: Rutin analizlerde kullanılan HbA1c kiti internal ve external kontrolleri yanısıra laboratuvar içi doğrulama validasyon çalışmaları testin geçerli kılma basamakları, doğruluk (accuracy) Kesinlik (presizyon) ve rapor aralığı işlemleri yapılmıştır.

Sonuç: Hastane tıbbi laboratuvarında HbA1c kitinin bu doğrulama ve geçerli kılma işlemlerini tüm basamakları yapılmış ve kayıt altına alınmıştır. Çalışmalar arası tekrarlanabilirlik (%CV) 0.88, Yöntem / referans materyali karşılaştırma (% Bias) 3.94 Hedef: (% Bias + 1.65 (%CV) < TEa) Sonuç olarak TAH:5,40< TEa:18 (rilibak) olarak hesaplanmıştır ve kit verifiye olmuştur. Diyabetik popülasyon taramasında kullanılacak olan kitin doğruluğu maliyetli ve yaygın bir hastalığın tedavi ve takibinde klinisyen öngörüsünü etkileyeceği için önemlidir.Tüm laboratuvarlar ticari kit olsun olmasın doğrulama işlemlerini laboratuvar güvenirliğini ve kalitesini artırmak adına yapmalıdır. Özellikle toplumu etkileyecek hastalıkların analizlerinde klinisyenlere doğru yön vermek adına yapılması zorunlu olmalıdır. Geniş popülasyonu etkileyecek uzun süreli çalışmalarda kullanılacak kitin doğrulama verilerinin araştırma verilerine eklenmesi de çalışmanın etkinliğini artıracaktır.

Anahtar kelimeler: Validasyon; verifikasyon; ölçüm belirsizliği; doğruluk; kesinlik; Diyabetes Mellitüs; HbA1c

Introduction

Verification and validation are two of the most confusing definitions. Verification is the process of error evaluation. In other words, validation focuses on analytical errors. The types of errors and how to identify these errors, what analytical procedures will be applied and how much data will be needed, what statistical procedures should be applied, and what the tolerable error size will be are included in the validation process. Validation is the process of proving that a process, system, equipment or method operates as expected and meets its intended use in the CLSI and ISO Definitions. Verification is defined as "the process of verifying by examining and obtaining positive evidence that shows that the specified goals have been achieved" [1, 2, 3].

Our hospital applied for TUSKA (Turkish Health Services Quality and Accreditation Institute) hospital accreditation in 2018. Among the accreditation laboratory criteria, method validation has been carried out in the ready-made commercial kits used in the laboratory within the scope of the criterion "SH.LH.04.03, validation/verification studies and continuous quality control procedures should be carried out for the reliability of test results" in the accreditation standards application guide in health[4].

The hospital has been holding the HIMSS level 7 full digital hospital certificate since 2016[5]. It has been revalidated 3 times since 2016 and has been validated. During this process, clinical decision support systems that provide added value to the physician and the laboratory, made with clinical units in a fully digital structure, and laboratory-clinical applications have been made within hospital information systems[6].

In the HIMSS-EMRAM validation processes, application examples regarding financial, temporal, service quality and reliability in the healthcare service provided by using the digital structure were presented to the HIMSS-EUROPA audit team as analysis. In these analyses, an in-laboratory validation study of the HbA1c commercial kit was conducted for a long-term study on patients diagnosed with diabetes who were admitted to the hospital and whose HbA1c value was 9.

Our hospital has carried out in-laboratory kit validation studies in accordance with 1 international (HIMSS-EMRAM) and 1 international (TUSKA) standards. The example here is the commercial kit validation study that will be used to screen patients with HbA1c values of 9 and above in patients admitted to the hospital after the digital structuring in HIMSS-EMRAM Standards.

Ready-made commercial kits are used in routine studies in most medical and non-medical laboratories globally. Although these kit methods are used, each laboratory must verify the performance of the testing system before reporting its results. Almost all of the test parameters used in hospital medical laboratories are ready-made commercial kits.

It means objective testing and written documentation of the suitability of the stages of a measurement for specified purposes. These are testing and measurement processes performed to determine the performance of a method. The method varies depending on multifactorial interactions.

(Laboratory conditions, device, chemical substance used, standard, operator experience, etc.) Each laboratory must determine the performance of the test and analysis results performed with the method under its own conditions[7].

Under what circumstances would method validation be needed:

When any method will be applied for the first time in a laboratory, when a change is made in the method being used, when a validated method will be used in another laboratory or when measurements will be made with a different person or a different device, if there is a change at the end of the control tests, a validation study of the test will be carried out before a new research. There is an indication.

In ISO 22000:2018, verification is defined as providing evidence that the specified conditions are met (8).

For the validity of a test to be used in the laboratory, the following must be done.

To confirm that the necessary conditions for the specific purpose are met after the examination and to provide evidence. Validation/verification studies must be carried out before a new method is put into routine use. These verification procedures need to be performed repeatedly in some cases.

There are many device changes, especially in medical laboratories where ready-made commercial kits are used, as there are kit tenders. For devices with frequent device changes, validation and verification should be carried out in case of changes in the basic chemicals for which the kits are prepared by the laboratory (in case of method change), personnel, or in cases where the method will be used. First time for any changes in the laboratory that could affect the results All laboratory branches play an active role in diseases and their accurate diagnosis, risk factors, and effective prophylactic and treatment of diseases. To achieve this role, effective implementation of a quality system is essential in every laboratory seeking accreditation [7]. Worldwide validity can be met by providing accreditation to ISO/IEC 17025 for testing and calibration laboratories and ISO 15189 for medical laboratories. It covers the managerial and technical capabilities of a laboratory. The hallmark of the accreditation process is method validation, verification and quality assurance[8,9].

Some definitions cover some calculations in procedures.

Accuracy: Deviation of the measured value from the calibrated value or true value.

Precision: The ability to obtain close values of measurement obtained by repeating with the same sample.

Precision: It is also the degree of closeness of the values of independent measurements under certain conditions. Uncertainty calculations were replaced by repeatability and reproducibility definitions. The definition of precision is defined as repeatability and reproducibility.

Measurement uncertainty: The parameter characterizing the distribution of values that accompany the measurement result and that can reasonably correspond to the quantity measured. It is also referred to as "the parameter associated with the measurement that defines the distribution of values associated with the measured quantity". In this regard, k=2 is taken for a Confidence Interval of approximately 95%.

Bias: The difference between the average measured value and the accepted value (i.e., the certified or nominal value) obtained from a large number of measurements. The concept of reality is expressed with bias

Accuracy and precision must be in accordance with the reference ranges given by the manufacturer and the patient population of the laboratory. For this purpose, method comparison must be performed to detect bias or inaccuracy, repetition studies must be performed to detect impression, linearity studies must be performed to determine the report range, and a review of reference values must be performed to verify the reference range[9-10,11].

For a test to be validated, the laboratory manager must perform and record these steps and document the conformity of the reference values in the manufacturer's prospectuses and books.

Material and Methods

The HbA1c Kit, which is a CE-approved ready-made commercial kit, was used in the hospital medical biochemistry laboratory as a qualitative measurement kit and its characteristics are stated in the "Method Approval Evaluation Form". The information is taken from the company kit prospectus. The validation for the HbA1c kit in our Hospital Medical Laboratory was planned and performed as follows. All data were recorded.

1. Level 2 Internal Quality Control Material was used as the reference material for intra-study repeatability. These data were recorded in the device memory as of 30.10.2022.

2. The % CV values taken when calculating the total error were calculated by using accuracy and inter-study reproducibility data. Internal quality control material was used as reference material. % CV is the absolute average of Level 1 and Level 2 studies. The values taken for these data are available on the Daily Internal Quality Control Screen between 16.10.2022 and 27.10.2022.

3. BIAS values were determined by taking the absolute average of the accepted and valid bias values of the 2022 external quality studies. The invalid and unacceptable values were removed.

4. Total Error (TE) was calculated with the following formula

%TAH=%CV X 1.65 + BIAS

These values were compared with the Total Acceptable Error (TAE) values published by international reference organizations (BV DESIRABLE, CLIA, RILIBAK, IPH BELGIUM, BV MINUMUM, RCPA, CFX, AAB) and the values that met the following equation

%TE<% TAE were verified for our laboratory.

5. Measurement uncertainty calculation was made by taking twice the absolute average of the reproducibility of Level 1 and Level 2 %CVs in studies

(ABSOLUTE (Level 1 %CV + Level 2 %CV)) / 2) X 2).

Expanded measurement uncertainty was used and the k value was taken as 2.

6. The test principle, sample type, reference range, analytical measurement range, clinical reportable range, analytical sensitivity, and interference data in the Method Approval Data Form were taken from the package inserts sent by the companies with the kits.

7. When controls with new lot numbers and different values are entered into the system (i.e., internal quality control screen), the system changes all the values in a retrospective fashion. For this reason, target values between studies and within studies do not match.

8. The documents used in the study are as follows.

a. Method Approval Data Form (Quantitative tests) x 2

b. Method Approval Evaluation Form

c. External quality BIAS values, our laboratory's TE and international TAE values table

d. Measurement Uncertainty Table

Results

Table 1. Within-run repeatability

Control Number	Target value	Mean	SD	CV%
Control 1	5.58	4.885	0.05275	1.0799
Control 2	9.35	9.369	0.08425	0.8999

Table 2. Inter-study reproducibility

Control Number	Target value	Mean	SD	CV%	% Bias
Control 1	5.58	5,607	0.06272	1.1187	-0,4839
Control 2	9.35	9.422	0,0619	0.6577	-0,7701

Table 3. Test verification final calculations

Within-run repeatability (% CV)	0.98
Inter-study reproducibility (%CV)	0.88
Method/Reference material comparison (% Bias)	3.94
TARGET: % Bias + 1.65 (%CV) < TEa	TAH:5,40< TEa:18 (rilibak)

Discussion

Some branches are indispensable for all clinicians, supporting diagnosis and guiding follow-up and treatment. Getting accurate data from these branches is very important in charting a path for self-diagnosis and follow-up.

Ready-made commercial kits are used in medical laboratories on a global scale. Although internal quality and external quality controls are used, laboratories can perform the validation and verification processes to control their own accurate measurement and reliability.

Like any other tests, the HbA1c ready-made commercial kit is regularly checked externally and internally and evaluated by laboratory specialists in the hospital medical laboratory. However, this is not sufficient for the reliability of the test. Validation and verification procedures must be performed for the test the laboratory will use.

Documenting the accuracy of a test to be performed before a study is conducted for the diagnosis and follow-up of a disease that is costly for the demographic structure of the entire society and the country is very important in evaluating the study data [12].

Complications such as retinopathy, neuropathy, and nephropathy may occur because of high blood sugar levels in diabetic patients. The multitude of complications is the reason for referral and examination to all branches. For this reason, early diagnosis and diabetes control reduces the relevant costs [13 (1),14].

This test provides benefits in many areas such as investigating the complications that are associated with high blood sugar levels, determining risk factors, and adjusting the insulin dose accordingly.The HbA1c Test is a common blood test used to diagnose and monitor Type 1 and Type 2 Diabetes. HbA1c Test means glycated hemoglobin, glucose-bound hemoglobin. HbA1c, but by internationally standardized methods

When measured, it can be used as a diagnostic test. In our country

Since HbA1c measurement tests have not been standardized yet, only

It is not recommended to be used as a diagnostic test on its own. In the presence of anemia, hemoglobinopathies, pregnancy (2nd and 3rd trimester), which affect some HbA1c

tests, patients who use antioxidants such as vitamins C and E should be excluded from the screening[16].

The HbA1c Test result shows the average blood sugar level over the last 3 months and measures how much erythrocytes are exposed to glucose and what percentage of the oxygen-carrying protein hemoglobin is bound to glucose.

Diabetes Mellitus is a very expensive disease, both in treatment and follow-up, due to multiorgan involvement in all countries and societies. Protective preventive actions become important in this disease, as it affects every branch due to complications. Chronic hyperglycemia causes long-term complications such as retinopathy, neuropathy, and nephropathy[17].

It often accelerates macro and micro vascular changes. Sedentary lifestyles around the world have made diabetes a global epidemic, and approximately 346 million people have been diagnosed with diabetes worldwide. In the cost analysis conducted in the USA, diabetes-related expenses constitute 1 out of every 7 dollars in the health budget [18,19].

Efficient and effective management is required to overcome this epidemic. Portable glucose meters facilitate short-term management of diabetes. Long-term prospective studies, particularly the Diabetes Control and Complications Trial (DCCT), the United Kingdom Prospective Diabetes Study Group (UKPDS) and the Epidemiology of Diabetes Interventions and Complications (EDIC) study, have provided conclusive evidence that diabetic complications are directly associated with diabetes. It refers to the glycemia value measured by HbA1c concentration

These types of disease groups, which affect large masses and whose treatment and follow-up are costly in terms of time and money, are important to guide clinicians. For this reason, the kit to be used in the analysis to be carried out in studies covering a long period of time and a large population must be validated, whether it is created under commercial or laboratory conditions. and its inclusion in the research would be more accurate in clinicians' approach to the disease.

Conclusion

In our hospital laboratory, validation, and verification studies were performed before the HbA1C screening study was planned together with public health. When the process steps were evaluated, the accuracy, precision, measurement range, and reference range of the method used were confirmed by our studies. Method validity was documented by meeting the abovementioned criteria

All laboratories must conduct pre-study validation studies and certify that the method is valid on their behalf, whether commercial or not. Internationally accredited laboratories around the world are indispensable analysis sources for all clinical branches and are used as references for every critical disease group. Every laboratory specialist aims to be in this group of laboratories.

The present study is a kit validation study conducted within the laboratory to verify whether the commercial kit purchased works correctly or not. For this reason, it is not included in the criteria requiring an ethics committee.

There is no institution or organization that financially supports the study.

Conflict of Interest

There is no conflict of interest

Ethics Committee

I hereby declare that, in accordance with the Personal Data Protection Law, retrospective studies are not among the studies that require an ethics committee and that they are not required.

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Research Article

Coronary computed tomographic angiography findings in diabetic patients: A tertiary clinic findings

Diyabetli hastalarda koroner bilgisayarlı tomografi anjiyografi bulguları: Üçüncü basamak klinik bulguları

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Abstract

Aim: The aim of this study is to identify different types of plaques in diabetic patients suspected of coronary atherosclerosis using coronary computed tomography angiography (CCTA) and assess the extent of coronary artery disease (CAD).

Material and Methods: Data from 252 diabetic patients who underwent CCTA were reviewed retrospectively. The mean age of the patients was 60 ± 10 years, and all underwent MSCT angiography. Plaque types were categorized into three groups: calcified, soft, and mixed. Statistical analyses were performed using SPSS v. 15.0 software.

Results: Of the 252 diabetic patients, 137 (54.4%) were male and 115 (45.6%) were female. CCTA detected stenosis ≥30% in 40 patients (15%). Calcified plaques (38%) and soft plaques (40%) were observed most frequently in the proximal LAD. CCTA results showed high sensitivity and specificity when compared to invasive angiography.

Conclusion: While invasive coronary angiography is considered the gold standard, coronary CTA is a reliable and non-invasive method for evaluating atherosclerosis in diabetic patients. Its high negative predictive value may be effective in ruling out bypass graft stenosis and can reduce the need for invasive procedures, minimizing patient risk.

Keywords: Diabet, plaque, angiography

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Öz

Amaç: Bu çalışmanın amacı, koroner ateroskleroz şüphesiyle değerlendirilen diyabetik hastalarda, koroner bilgisayarlı tomografi anjiyografi (CCTA) kullanarak farklı plak tiplerini tanımlamak ve koroner arter hastalığının (KAH) kapsamını değerlendirmektir.

Gereç ve Yöntemler: CCTA uygulanan 252 diyabetik hastanın verileri retrospektif olarak incelendi. Hastalara CT anjiyografi uygulandı. Plak tipleri, kalsifiye, yumuşak ve miks olmak üzere üç gruba ayrıldı. İstatistiksel analizler SPSS v. 15.0 yazılımı ile yapıldı.

Bulgular: Toplamda 252 diyabetik hastanın 137'si (%54,4) erkek, 115'i (%45,6) kadındır. CCTA, %30 ve üzeri darlık bulunan 40 hastada %15 oranında stenoz bulguları tespit etti. En çok kalsifiye (%38) ve yumuşak plaklar (%40) proximal LAD'de gözlemlendi. Koroner anjiyografi sonuçları ile CCTA'nın bulguları karşılaştırıldığında, CCTA'nın tespit ettiği progresyonlar arasında yüksek bir duyarlılık ve özgüllük olduğu görüldü.

Sonuçlar: İnvaziv koroner anjiyografi altın standart olarak kabul edilse de , koroner CCTA, diyabetik hastalarda aterosklerozun değerlendirilmesi için güvenilir ve non-invaziv bir yöntemdir. CCTA'nın yüksek negatif prediktif değeri, bypass greft stenozunu dışlamakta etkili olabilir ve invazif prosedür gereksinimini azaltarak hasta riskini minimize edebilir.

Anahtar kelimeler: Diyabet, plak, anjiografi

Introduction

Coronary atherosclerosis is recognized as a leading cause of morbidity and mortality in industrialized countries. Diabetes is one of the well-known risk factors for the development of coronary artery disease (CAD) (1). Myocardial infarction occurs at an earlier age and is more recurrent in diabetic patients (2). Between 65-75% of patients with type 2 diabetes succumb to cardiovascular disease (3). The mortality rate of a diabetic patient who experiences an acute coronary event is >50% compared to a non-diabetic patient (4).

Silent ischemia is commonly observed in diabetic patients; the lack of symptoms leads to delayed diagnosis and makes it difficult to detect ischemia (5). Additionally, coronary disease in diabetic patients is more diffuse and has more distal localization, complicating revascularization (6).

Furthermore, diabetes worsens the prognosis in both the early and late stages of acute coronary syndrome. The presence of diabetes increases the risk of myocardial infarction, complications, and mortality during hospitalization (7). Compared to non-diabetic patients, the success rate of coronary interventions is lower in diabetic patients (8). Understanding the plaque characteristics seen in diabetic and non-diabetic patients and guiding risk factor modification is crucial in the approach to coronary artery disease (9).

Coronary computed tomography angiography (CCTA) is a valid imaging method for evaluating known or hidden coronary artery disease (10). Thus, CCTA can be useful in investigating the risks of asymptomatic diabetic individuals.

Our study aimed to identify the different types of plaques in diabetic patients who are either suspected of having coronary atherosclerosis, have undergone bypass surgery, or have received stents. Additionally, we sought to assess the extent of coronary artery disease in these patients using CCTA.

Material and Methods

The data of 252 diabetic patients who underwent coronary computed tomography angiography (CCTA) at Hacettepe University Faculty of Medicine, Department of Radiology, between April 2007 and January 2008, due to suspected coronary artery disease (CAD) or suspicion of progression of previously diagnosed CAD, were retrospectively reviewed. The study protocol was approved by the local ethics committee of Hacettepe University Faculty of Medicine (Ethics Committee No: 2010-10/38). All patients underwent coronary MSCT angiography. The angiography reports of 64 patients who had also undergone invasive coronary angiography were retrospectively reviewed and compared with the CCTA results. Inclusion criteria were adult individuals (age ≥ 18 years) diagnosed with diabetes mellitus, those who underwent CCTA for the evaluation of suspected CAD or for follow-up of previously diagnosed CAD, individuals with a history of coronary artery bypass graft surgery or stent placement. Exclusion criteria included patients with a documented severe allergy to iodinated contrast agents, those with renal insufficiency (glomerular filtration rate < 60 mL/min/1.73 m^2) that precluded the use of contrast media, pregnant women due to potential radiation risks, patients with non-diabetic etiology of atherosclerosis" method bölümüne eklendi (satır numarası 191).

All cardiac CT examinations were performed using a dual-source 64-slice CT scanner (SOMATOM Definition, Siemens

Medical Solutions, Forchheim, Germany). The gantry rotation time was 330 ms, the slice and detector thickness were 0.6 mm, the reconstruction interval was 0.6 mm, and the detector configuration was 2x32x0.6 mm. The pitch was automatically adjusted by the device according to the heart rate. An 18-20 gauge intravenous line was inserted into the patients before the examination, and their heart rates and rhythms were monitored using an ECG. Following the acquisition of a scanogram, a section passing through the level of the aortic root was obtained, and the bolus tracking method (CARE Bolus, Siemens Medical Solutions, Forchheim, Germany) was used by placing the region of interest (ROI) in the aortic root. Through an intravenous route, 100 ml of non-ionic contrast agent was administered at a rate of 5-6 ml/sec using an automatic injector (Ulrich, Germany). Data acquisition commenced when the ROI reached a density of 100 HU. Routine coronary CT angiography involved scanning from the level of the carina to the diaphragm in coronary CT angiography patients, and from the thoracic inlet to the diaphragm in examinations conducted for bypass assessment. Retrospective ECG-gated algorithms optimized for MSCT were used for raw data reconstruction. All coronary CT angiography examinations were completed without complications.

Coronary and bypass CT angiography examinations were conducted using 3-D software on a LEONARDO (Siemens) workstation. Each lesion was identified using multi-planar reconstruction (MPR) techniques and maximum intensity projection (MIP) in the transverse and axial planes.

Plaques were defined as structures larger than 1 mm in or adjacent to the vessel lumen, easily distinguishable from the lumen and surrounding pericardial structures. Atherosclerotic plaques were categorized into three groups: calcified, soft, and mixed.

The degree of coronary artery stenosis was classified as normal (0-29%), mild (30-49%), moderate (50% and above), and severe. A reduction in vessel diameter of more than 50% was considered significant stenosis. Vessel occlusion was defined as the complete interruption of luminal passage visible by contrast enhancement.

Statistical Analysis

In our study, qualitative data were described using numbers and percentages. For continuous numerical data, mean and standard deviation (mean ± SD) were used to describe normally distributed continuous variables, while median and interquartile range (IQR 25 and 75) were used for variables that did not follow a normal distribution. Normality was assessed using the Kolmogorov-Smirnov test. For values given as mean and standard deviation, either the independent samples t-test or one-way analysis of variance (ANOVA) was used, depending on the number of groups being compared. For values given as medians, the Mann-Whitney U test or Kruskal-Wallis test was used. For the analysis of categorical data, the chi-square test was employed, and Fisher's exact chi-square test was used when necessary, depending on sample size. Linear relationships among all variables measured continuously were examined. Pearson correlation coefficients were used for normally distributed variables, and Spearman correlation coefficients were used for non-normally distributed variables. The correlation coefficient was denoted by 'r,' and the significance value was denoted by 'p.' The data were analyzed using the SPSS v. 15.0 software package.

Results

Of the 252 diabetic patients included in our study, 137 (54.4%) were male and 115 (45.6%) were female. The patients' ages ranged from 28 to 86 years, with a mean age of 60 ± 10 years. There were 67 patients (26.6%) with bypass surgery, 26 patients (10.3%) with stents, and 8 patients (3.2%) with both stents and bypass surgery. A total of 151 patients had neither bypass nor stents. All patients underwent CTA. Among these, 30 of the patients without bypass or stents, 19 with bypass, and 12 with stents underwent invasive angiography (Figure 1 and 2). In 40 (15%) of the 252 diabetic patients, at least 30% stenosis was detected in 1 coronary artery; in 32 (12.7%) patients, stenosis was detected in 2 arteries; in 34 (13.5%) patients, in 3 arteries; in 12 (4.8%) patients, in 4 arteries; and in 1 (4%) patient, in 5 coronary arteries. In 133 (52.8%) patients, stenosis was found to be less than 30% (Table 1).

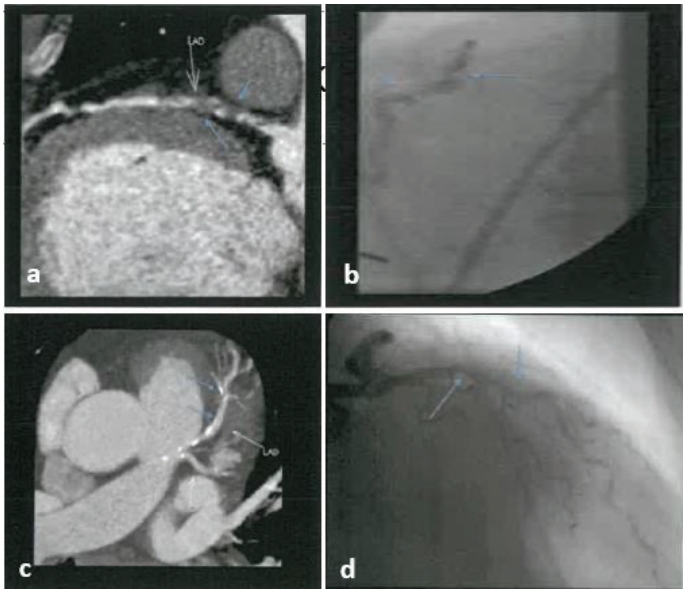

Figure 1. (a). The appearance of soft plaques observed in the proximal LAD on CT coronal images is shown. **(b)** The angiographic appearance of the stenosis caused by soft plaques in the LAD of the same patient is demonstrated. **(c)** Mixed type plaques are observed in MIP images in the LAD. **(d)** The appearance of stenosis caused by mixed-type plaques in the same patient on invasive angiography is demonstrated.

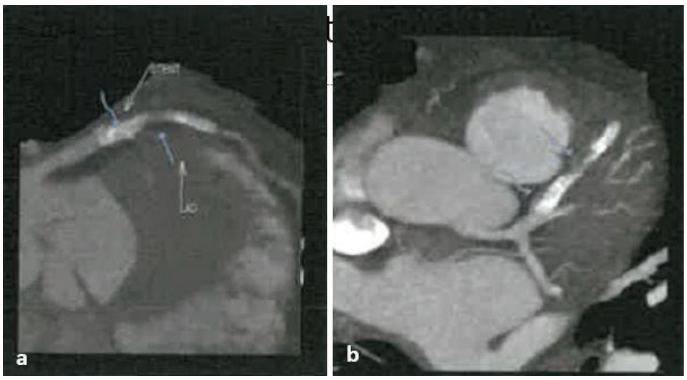

Figure 2. (a). There is soft plaque and intimal hyperplasia in the proximal stent (curved arrow). Dense atheroma plaques and critical stenosis are observed between the two stents.**(b)** The MIP reformat image of the same patient is shown. In MIP images, two stents placed in the LAD are observed. There is soft plaque and intimal hyperplasia in the proximal stent (curved arrow). On the appearance of dense atheroma plaques and critical stenosis between two stents (solid arrow)

Table 1. Important demographic characteristics of patients	
Female	115 (%‹›45.6)
Male	137 (%54.4)
Age (year)	60+10
HDL (mg/dl)	49+13
LDL (mg/d1)	109+40
TG (mg/d1)	182+42
VKI (kg/m2)	28+4.9
BMI: Body mean index,HDL: High density lipoprotein, LDL: Low density lipoprotein, TG: Trigliserit	

Among the 151 patients without bypass or stents who were suspected of having coronary artery disease, coronary CTA revealed atherosclerosis in 91 patients, while 60 patients were evaluated as normal. Invasive angiography was performed in 30 of these 91 patients to determine treatment protocols. Of these patients, 6 had mild stenosis on CTA, and mild stenosis was confirmed in 4 patients on invasive angiography. Among the 6 patients with moderate stenosis on CTA, 5 were found to have moderate stenosis on invasive angiography. Advanced stenosis was confirmed in 12 of the 16 patients with more than 50% stenosis on CTA. Nine patients were evaluated as normal on invasive angiography.

Invasive angiography confirmed normal coronary arteries in 3 of the 60 patients with normal CTA results. The distribution of plaque types in different regions for the 91 diabetic patients with atherosclerosis, out of the 151 patients without bypass or stents (Table 2). In these 91 patients, the number of calcified plaques was 115 (38%), soft plaques were 124 (40%), and mixed plaques were 68 (22%). Calcified and soft plaques were most frequently observed in the proximal LAD, while mixed plaques were most frequently observed in the mid-LAD.

Invasive angiography was performed on 19 patients with bypass surgery. In 11 patients whose bypass vessels were open on coronary CTA, the invasive angiography results were also normal. In 6 patients with occlusion in one bypass vessel on CTA, invasive angiography confirmed the occlusion in 5 patients, while the stenosed graft could not be demonstrated in one patient. In 2 patients with occlusion in two bypass vessels on CTA, invasive angiography confirmed the occlusion in both bypass vessels.

Of the 26 patients with stents, the stents were optimally evaluated on coronary CTA in 24 patients. Among these, 20 patients (77%) had normal findings on CTA, 2 patients (7%) had intimal hyperplasia, 1 patient (4%) had mild stenosis, and 1 patient (4%) had moderate stenosis. Invasive coronary angiography was performed on 12 of the 26 patients with stents following coronary CTA. The sensitivity and specificity of coronary CTA in detecting stenosis were found to be 80% and 100%, respectively (Table 3).

Discussion

Conventional coronary angiography remains the gold standard for evaluating coronary artery disease (CAD). However, increasing evidence suggests that coronary angiography has inherent limitations as it only visualizes the lumen (10). These limitations are primarily due to coronary artery remodeling and diffuse coronary atherosclerosis (11).

Coronary CTA, on the other hand, can visualize both the lumen and the vessel wall, allowing for the diagnosis of early atherosclerotic disease before stenosis occurs. Due to anatomical changes, the difficulty in catheterizing grafts reduces the success of invasive angiography in evaluating bypass grafts. Coronary CTA, unaffected by these anatomical changes, provides a high sensitivity and specificity in evaluation (12-15).

In the study by Weustink et al., 52 patients with symptoms post-bypass surgery underwent CTA followed by invasive coronary angiography, with CTA showing a 100% accuracy in detecting or ruling out significant stenosis in arterial and venous grafts (16). Nieman et al. evaluated 24 patients with bypass surgery using MDCT and demonstrated high sensitivity and specificity for detecting graft stenosis. Sensitivity and specificity were 100% and 96% for venous graft occlusion, 100% and 85.7% for venous graft stenosis, and 100% and 100% for arterial graft stenosis, respectively (17).

Table 2. Distribution of plaque types by region in 91 diabetic patients with suspected coronary artery disease and atherosclerosis

	Calsific		Soft		Mix		Total	
	number	%	number	%	number	%	number	%
LM	15	9.7	4	2.6	5	3.2	24	15,5
LAD proximal	22	14.2	24	15.5	12	7.7	58	35.4
LAD middle	14	9	23	14.8	14	9	51	37.4
LAD distal	9	5.8	5	3.2	6	3.9	20	12.9
Diagonal	9	5.8	7	4.5	4	2.6	20	12.9
RCA proximal	11	7.1	8	5.2	6	3.9	25	16.2
RCA middle	10	6.5	12	7.7	8	5.2	30	19,4
RCA distal	7	4.5	8	5.2	4	2.6	19	12.3
circumflex proximal	9	5.8	13	8.4	2	1.3	24	15.5
circumflex middle	8	5.2	14	9	4	2.6	26	16.8
circumflex distal	1	0.6	6	3.9	3	1.9	10	6.4
Total	115	74.2	124	80	68	43.9	307	

LAD: Left anterior descending artery, RCA: Right coronary artery

Table 3. Distribution of plaques according to regions and degrees of stenosis in 26 patients with stents

	Mild		Moderate		Severe		Normal	
	number	%	number	%	number	°Z»	number	°Z»
LM	4	14.3	0	0	0	0	24	85.7
LAD proximal	7	25	2	7.1	3	10.7	16	57.1
LAD middle	4	14.3	3	10.7	6	21.4	15	53.6
LAD distal	4	14.3	1	3.6	4	14.3	19	67.9
Diagonal	4	14.3	1	3.6	1	3.6	22	78.6
RCA proximal	I	3.6	3	10.7	4	14.3	20	71.4
RCA middle	1	3.6	3	10.7	3	10.7	21	75
RCA distal	1	3.6	3	10.7	0	0	24	85.7
circumflex proximal	7	25	2	7.1	3	10.7	16	57.1
circumflex middle	2	7.1	0	0	4	14.3	22	78.6
circumflex distal	I	3.6	0	0	1	3.6	26	92.9

LAD: Left anterior descending artery, RCA: Right coronary artery

In a study by Ropers et al. evaluating a total of 182 grafts in 65 patients, similar to Nieman et al.'s results, graft occlusion was detected with 97% sensitivity and 98% specificity (18). In our study, all patients with bypass surgery who had normal findings on coronary CTA were confirmed to have normal findings on invasive angiography.

In a study by Mollet et al. involving diabetic patients with stable coronary artery disease, 24% of the patients had soft plaques, and 65% had calcified plaques on MDCT. Soft plaques, mostly non-obstructive, were observed in asymptomatic individuals, whereas calcified plaques were more common in symptomatic patients (19). Raggi et al. found that soft plaques were associated with the rate of cardiac events in a study involving 903 asymptomatic diabetic patients (20). In our study, the rates of calcified, soft, and mixed plaques were found to be 38%, 40%, and 22%, respectively.

In the study by Das et al., coronary CTA was performed after invasive coronary angiography on 53 patients with stents, correctly identifying restenosis in 91% of 107 stents (21). In a study by Libague et al. involving 47 patients with a total of 72 coronary lesions, coronary CTA and invasive angiography findings were compared post-stent placement. They concluded that MDCT more easily demonstrated stent lumens and stent kinks compared to invasive angiography (22). In our study, the stents in 24 of the 26 patients with stents were optimally evaluated by coronary CTA. Of these patients, 20 (77%) had normal findings on CTA, while 2 patients (7%) had intimal hyperplasia, 1 patient (4%) had mild stenosis, and 1 patient (4%) had moderate stenosis. Invasive coronary angiography was performed on 12 of the 26 patients with stents following coronary CTA. The sensitivity and specificity of coronary CTA in detecting stenosis were found to be 80% and 100%, respectively.

The 2016 guidelines from the Society of Cardiovascular Computed Tomography (SCCT) and the North American Society for Cardiovascular Imaging (NASCI) affirm that coronary CTA is a reliable, non-invasive diagnostic tool for assessing coronary artery disease. It provides high diagnostic accuracy for evaluating both acute and stable chest pain syndromes (23).

In our study, we offer a detailed characterization of plaque types (calcified, soft, and mixed) in diabetic patients, highlighting the importance of early detection of non-calcified and mixed plaques which can precede acute coronary syndromes . Unlike existing literature that predominantly emphasizes calcified plaques, our findings bring attention to the considerable presence of soft and mixed plaques, thereby providing a novel viewpoint in this area. Secondly, we demonstrate that CTA is a reliable method with a high negative predictive value, making it a safer alternative to invasive coronary angiography, especially beneficial for diabetic patients who are at high risk. Moreover, The comparison of CTA with invasive angiography in our study underscores the high sensitivity and specificity of CTA in detecting stenotic lesions, supporting its use in clinical practice to reduce the necessity for invasive procedures and thus minimizing patient risk (24).

This study's retrospective design may introduce selection bias, limiting the applicability of the findings to the broader diabetic population. Conducted at a single center, it may lack sufficient diversity, and the reliance on contrast-enhanced imaging poses risks for patients with renal impairment. Additionally, the study did not evaluate the long-term outcomes of plaque types identified by CCTA, indicating a need for future multicenter, prospective studies to address these limitations.

Although invasive coronary angiography is still considered the gold standard for evaluating graft patency and stenosis, it is an invasive procedure with potential complications such as arrhythmia, graft dissection, myocardial infarction, and embolism. Studies comparing 64-slice CT and invasive coronary angiography for evaluating coronary graft patency and stenosis have shown that 64-slice CT is a reliable and less invasive method than coronary angiography (25-27).

Conclusion

While invasive coronary angiography remains the gold standard for evaluating coronary artery disease, it is an invasive method. Coronary CTA is a reliable method for evaluating stent lumens. Coronary CTA is a non-invasive, reliable method that can be used to evaluate diabetic patients with suspected atherosclerosis, stents, and bypass grafts. It has a high negative predictive value for assessing stent patency. We believe that CTA is also useful in ruling out bypass graft stenosis in patients.

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Conflict of interest

The authors declare that they have no conflict of interest.

Compliance with Ethical Standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval obtained from a local commitee.The ethics committee waived the need for consent because it was a retrospective study

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Research Article

Antimicrobial effects of ropivacaine, levobupivacaine and bupivacaine at different temperatures

Ropivakain, levobupivakain ve bupivakainin farklı sıcaklıklardaki antimikrobiyal etkileri

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Abstract

Aim: Various prior studies have shown a possible antimicrobial activity of different local anesthetic (LA) drugs. The aim of this study was to assess the antimicrobial (antibacterial or antifungal) activity of commonly used commercially available LA drugs used in regional anesthesia practice such as; ropivacaine, levobupivacaine and bupivacaine on S.aureus ATCC 6538, S. epidermidis, E.coli and Candida albicans at different temperatures.

Material and Methods: Possible antimicrobial effects of ropivacaine (1% and 0.125%), levobupivacaine (0.75% and 0.125%) and bupivacaine (0.5% and 0.125%) on S.aureus ATCC 6538, S.epidermidis, E.coli and C.albicans ATCC 10231, which were isolated from patients in the microbiology laboratory were investigated at 24°C and 37°C.

Results: All three LA drugs showed antifungal activity at 37°C and 24°C in 3rd and 12th hours. Levobupivacaine's (0.75%) antibacterial effect was observed at the 12th hour. Ropivacaine (1%) had relatively more antibacterial effect at the 3rd and 12th hour at 37°C rather than 24°C whereas bupivacaine had less.

Conclusion: Potential clinical implications of antibacterial or antifungal effects of local anesthetics might be promising.

Keywords: Local anesthetics, bupivacaine, levobupivacaine, ropivacaine, Antimicrobial activity, antibacterial, antifungal

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Öz

Amaç: Lokal anestezik (LA) ilaçların, daha önce yapılan çeşitli çalışmalarla olası bir antimikrobiyal aktivitesi gösterilmiştir. Bu çalışmanın amacı, rejyonel anestezi uygulamalarında yaygın olarak kullanılan ropivakain, levobupivakain ve bupivakain gibi ticari olarak mevcut LA ilaçlarının farklı sıcaklıklarda S.aureus ATCC 6538, S. epidermidis, E.coli ve Candida albicans üzerindeki antimikrobiyal (antibakteriyel veya antifungal) aktivitesini değerlendirmektir.

Gereç ve Yöntemler: Mikrobiyoloji laboratuvarında ropivakain (%1 ve %0,125), levobupivakain (%0,75 ve %0,125) ve bupivakainin (%0,5 ve %0,125) hastalardan izole edilen S.aureus ATCC 6538, S.epidermidis, E.coli ve C.albicans ATCC 10231 üzerindeki olası antimikrobiyal etkileri 240C ve 370C'de araştırıldı.

Bulgular: Her üç lokal anestezik ilaç da, 37°C ve 24°C'de 3. ve 12. saatlerde antifungal aktivite göstermiştir. Levobupivakainin (%0,75) antibakteriyel etkisi 12. saatte gözlendi. Ropivakain (%1) 37°C'de 3. ve 12. saatlerde 24°C'ye göre nispeten daha fazla antibakteriyel etkiye sahipken, bupivakain daha az antibakteriyel etkiye sahipti.

Sonuçlar: Lokal anesteziklerin antibakteriyel veya antifungal etkilerinin potansiyel klinik sonuçları umut verici olabilir.

Anahtar Kelimeler: Lokal anestezikler, bupivakain, levobupivakain, ropivakain, Antimikrobiyal aktivite, antibakteriyel, antifungal

Introduction

In clinical practice local anesthetic (LA) drugs are used not only to provide analgesia and/or anaesthesia but also to treat arryhthmias. However, various studies have shown possible antimicrobial activity. A number of studies reported that bupivacaine (0.25%), lidocaine (1.25%) and chloroprocaine (0.75%) inhibited growth of Staphylococcus aureus (S.aureus), whereas articaine, bupivacaine and ropivacaine have shown relatively weak antibacterial effect on skin flora bacteria like Escherichia coli (E.coli), S.aureus and Pseudomonas aeruginosa (P.aeruginosa) [1-4]. Since we have not come across any comprehensive research investigating the relationship between antimicrobial activity of LA drugs and temperature until now, we hypothetize whether anesthetic and/or analgesic concentration of LA drugs might have a possible antimicrobial effect against fungus and/or bacteria at 37°C rather than room temperature which could be a potential implication in regional anesthesia practice. Therefore, we aimed to investigate the possible antimicrobial (either antibacterial or antifungal) activity of clinically used concentrations of ropivacaine, levobupivacaine and bupivacaine on S. aureus ATCC 6538, S. epidermidis, E.coli and Candida albicans at different (either room or body) temperatures. Secondly, to indicate the survivability of the possible antimicrobial effect.

Material and Methods

After obtaining approval of the institutional ethic committee for in vitro investigations, possible antimicrobial effects of ropivacaine (1% and 0.125%) levobupivacaine (0.75% and 0.125%) and bupivacaine (0.5% and 0.125%) on S. aureus ATCC 6538, S. epidermidis, E. coli and C.albicans ATCC 10231, which were isolated from patients' blood samples in the microbiology laboratory at 240C and 370C for accepted as room and body temperatures, respectively were investigated.

Experiment Protocol

1st step: Selection of LA drugs and concentration

Commercially available LA drugs (ropivacaine 1%, bupivacaine 0.5% and levobupivacaine 0.75%) were chosen and their original concentrations and 0.125% concentraions were investigated.

1. Ropivacaine (Naropin®Ampule 1%, 20 mL injektions-lösung, AstraZeneca) 1% and 0.125%.

2. Levobupivacaine (Chirocaine® Ampule, 0.75%, 10 mL, Abbott) 0.75% and 0.125%.

3. Bupivacaine (Marcaine® 0.5%, injection solution flacon 20 mL, AstraZeneca) 0.5% and 0.125%.

Step 2: Selection of Microorganisms (0.5 Mc Farland)

1. Staphylococcus aureus ATCC 6538

2. Staphylococcus epidermidis

3. Escherichia coli

4. Candida albicans ATCC 10231 were chosen.

Step 3: Procedure

Nutrient broth medium was placed in each tube. Samples of S. aureus, S. epidermidis, E. coli and C. albicans were prepared with bacterial and yeast suspensions of 0.5 McFarland each. Three bacteria strains (S. aureus, S. epidermidis and E. coli) and

1 fungus (C. albicans) and their control groups were prepared.

Total of 56 samples were studied at room and body temperatures:

Ropivacaine 2 concentrations X 4 microorganisms (n=8)

Levobupivacaine 2 concentrations X 4 microorganisms (n=8)

Bupivacaine 2 concentrations X 4 microorganisms (n=8)

Study Group 24 oC (n=24) and Control Group 24 oC (n= 4)* (24+4=28)

Study Group 37 oC (n=24) and Control Group 37 oC (n= 4)* (24+4=28)

*: 1 control sample for each microorganism

Tubes from the study and control groups were kept at 24°C and 37°C for each incubation time period (3th hour, 12 hour and 24 hour), then samples were taken from the nutrient agar medium. Petri dishes were divided into 4 sections and 5µL of each LA drug was inoculated. Each drug was studied in the incubator, which corresponds to either room or body temperature (Figure A and B).

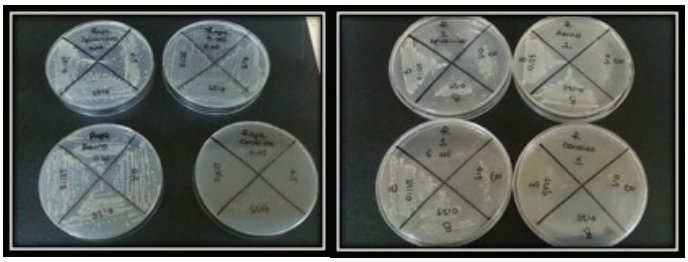

Figure 1.A-B. Incubated petri dishes containing different concentration of local anesthetics.

After incubation in incubator for 24 hours, all the plaques were evaluated whether there was a growth or not. In case of no growth which was represented as negative effect (-), antibacterial effect was considered for that local anesthetic. If there was a growth which was represented as positive (+), there was no antibacterial effect. More extensive growth was indicated with ++.

Statistical Analysis

Sample size was calculated according to the investigation of 40 bacterial isolates for 3 LA drugs as described [5]. IBM SPSS® Statistics (Statistical Package for the Social Sciences) for Windows 23 program was used. Results were expressed in numbers or percentages where appropriate. Reproductive findings were accepted as categorical variables and presence of growth were compared according to temperatures (24ºC vs 37ºC) with chi-square test using Epi info programme. A p value of less than 0.05 was considered as statistically significant.

Results

Antibacterial effects of three LA drugs; 3, 12 and 24 hours after incubation were presented at room (24°C) and body (37°C) temperatures (tables 1, 2 and 3).

Ropivacaine 1% showed antibacterial effect against S.aeurus and E.Coli at 37°C 3 hours after incubation (Table 1). Ropivacaine 1%'s antibacterial activity showed statistically significant difference between 24ºC and 37ºC (p=0.03) but that effect was not significantly different when compared to 0.125% concentration at 37ºC (p=0.083). Bupivacaine 0.5% inhibited the growth of S.aureus 3 hours after incubation at 37ºC which did not significantly differ between 24ºC and 37ºC (p=0.30)(Table 1).

After 12 hours, ropivacaine 1% at 37°C and levobupivacaine 0.75% at both 24°C and 37°C showed antibacterial effect against S.aeurus, s.epidermidis and E.coli (Table 2).

After 24 hours, antibacterial effect of ropivacaine 1% against S.aeurus and s.epidermidis was observed at 24°C and 37°C, while it was observed against E.coli only at 24°C. Levobupivacaine 0.75% at 24°C showed antibacterial effect against only S.aeurus 24 hours after incubation and this effect was not statistically significant between 0.75% and 0.125% of levobupivacaine (p=0.223). When temperatures were compared; ropivacaine, bupivacaine and levobupivacaine's antimicrobial effects were not significant between 24ºC and 37ºC (p=0.068, p>0,05 and p=0.39, respectively) (Table 3).

The three local anesthetics at studied concentrations inhibited fungus growth at 37°C and 24°C until 3 and 12 hours after incubation (tables 4A and 1B).

Discussion

We observed that antimicrobial effects of LA drugs varied according to temperature and determination time after incubation. Hereby, ropivacaine 1% at 37°C and levobupivacaine 0.75% at both studied temperatures (24°C and 37°C) showed antibacterial effect against to all studied bacteria (S.aeurus, s.epidermidis and E.coli) 12 hours after incubation. Additionally, three LA drugs both at room and body temperatures exhibited antifungal action for 12 hours independent of the concentrations used in the present study.

Various studies reported that LA drugs could be regarded as antimicrobial agents [6-11]. Bactericidal activity of preservative free bupivacaine in the skin flora and in vitro comparison of antibacterial activity of bupivacine vs levobupivacaine and ropivacaine vs bupivacaine have been demonstrated [6,7,11].

Table 1. Bacterial growth 3 hours after incubation according to temperature and concentration of local anesthetics.

	Concentration	1%		0.75%		0.5%		0.125%	
	Temperature	24°C	37°C	24°C	37°C	24°C	37°C	24°C	37°C
Ropivacaine	S. aeurus	+	-*					+	+
	S. epidermidis	+	+					+	+
	E. coli	+	-*					+	+
Levobupivacaine	S. aeurus			+	+			+	+
	S. epidermidis			+	+			+	+
	E. coli			+	+			+	+
Bupivacaine	S. aeurus					+	-	+	+
	S. epidermidis					+	+	+	+
	E. coli					+	+	+	+

*:p <0.05 No growth (-), which means antibacterial effect for that local anesthetic.
Presence of growth (+), which means no antibacterial effect for that local anesthetic.
*p=0.03 Ropivacaine 1%'s antibacterial activity showed statistically significant difference between 24°C and 37°C.
p=0.083 Ropivacaine 0.125%'s antibacterial activity did not showed statistically significant difference between 24°C and 37°C.

Table 2. Bacterial growth 12 hours after incubation according to temperature and concentration of local anesthetics.

	Concentration	1%		0.75%		0.5%		0.125%	
	Temperature	24°C	37°C	24°C	37°C	24°C	37°C	24°C	37°C
Ropivacaine	S. aeurus	+	-					+	+
	S. epidermidis	+	-					+	+
	E. coli	+	-					+	+
Levobupivacaine	S. aeurus			-	-			+	+
	S. epidermidis			-	-			+	+
	E. coli			-	-			+	+
Bupivacaine	S. aeurus					+	+	+	+
	S. epidermidis					+	+	+	+
	E. coli					+	+	+	+

*:p <0.05
No growth (-) means antibacterial effect for that local anesthetic.
Presence of growth (+) means no antibacterial effect or that local anesthetic.

Table 3. Bacterial growth 24 hours after incubation according to temperature and concentration of local anesthetics.

	Concentration	1%		0.75%		0.5%		0.125%	
	Temperature	24°C	37°C	24°C	37°C	24°C	37°C	24°C	37°C
Ropivacaine	S. aeurus	-	-					+	+
	S. epidermidis	-	-					+	+
	E. coli	-	+					+	+
Levobupivacaine	S. aeurus		-	+			+	+	
	S. epidermidis		+	+			+	+	
	E. coli		+	+			+	+	
Bupivacaine	S. aeurus			+	+	+	+		
	S. epidermidis			+	+	+	+		
	E. coli			+	+	+	+		

No growth (-) means antibacterial effect for that local anesthetic.
Presence of growth (+) means no antibacterial effect or that local anesthetic.

Table 4A. Fungal (C. albicans) growth at room and body temperatures 3 and 12 hours after incubation of varying concentrations of local anesthetics.

Concentration	0.125%		0.5%		0.75%		1%	
Temperature	24oC	37oC	24oC	37oC	24oC	37oC	24oC	37oC
Bupivacaine	-	-	-	-				
Levobupivacaine	-	-	-	-	-	-		
Ropivacaine	-	-	-	-	-	-	-	-

In case of no growth which was represented as negative effect (-), it was considered that there was an antibacterial effect for that local anesthetic. If there was a growth which was represented as positive (+), it was considered that there was no antibacterial effect.

Table 4B. Fungal (C. albicans) growth at room and body temperatures 24 hours after incubation according to concentration of local anesthetics.

	Temperature	
	24ºC	37ºC
Bupivacaine (0.5%, and 0.125%)	+	+
Levobupivacaine (0.75%, and 0.125%)	++	+
Ropivacaine (1%)	-	+
Ropivacaine (0.125%)	+	+

In case of no growth which was represented as negative effect (-), it was considered that there was an antibacterial effect for that local anesthetic. If there was a growth which was represented as positive (+), it was considered that there was no antibacterial effect.

Additionally, bacterial growth was observed with ropivacaine hydrochloride of 10 mg/mL (not with 2 mg/mL), ropivacaine 1% with sufentanil inhibited in vitro growth of p.aeruginosa [9, 10]. However, levobupivacaine 1% with sufentanil had no antibacterial effect at 25ºC in vitro [8]. Modification of the antibacterial activity of bupivacaine and ropivacaine was investigated in another study. Both bupivacaine and ropivacaine alone or with sufentanil inhibited growth of E.coli and S.aureus. The possible synergistic and/or antagonistic effect of sufentanil on the antibacterai activity of these two LA drugs could be mediated via the interaction of sufentanil with the cytoplasmic membrane where LA drugs act [12]. Therefore, we investigated local anesthetics' possible antimicrobial effect without adding any adjuvants.

In a previous study temperature and concentration dependent bactericidal activity against S. epidermidis and E.coli (skin flora bacteria) was observed with preservative free bupivacaine concentrations of 0.75%, 0.5%, 0.25% and 0.125% [6]. In another study, minimum bactericide concentration 24 hours after incubation for S. epidermidis, S. aureus and E. faecalis at 37oC for 0.125%, 0.25% and 0.5% concentrations of bupivacaine and levobupivacaine was found to be 0.25% for bupivacaine while it was 0.5% for levobupivacaine [7]. In contrast to these findings, not only bupivacaine 0.5% inhibited the growth of S.aureus at body temperature (37°C) but also ropivacaine 1% showed antibacterial effect against to S.aeurus and E.coli in our study. We chose to investigate anesthetic (0.5%) and analgesic (0.125%) concentrations to find out which concentration might produce antimicrobial effect. In regional anesthesia practice, the antimicrobial effect of the 0.5% concentration of bupivacaine against S. aureus (skin flora bacteria as well) at 37°C might have a protective role during disinfection.

Antibacterial effect of epidural infusion was studied in vitro because of the possible association with epidural abcess although it is a very rare (1 in 1000) complication [13]. It was reported that after 24 h incubation, inhibiton of growth was seen in 0.25% dilution prepared from bupivacaine 0.5% [2]. Regarding microorganisms associated with spinal/epidural abcess, inhibition of the growth of S.aureus with sufficient concentration of bupivacaine could explain very low incidence of epidural abcess as reported [2].

Despite to the early reports claming neither in vivo antimcirobial activity with bupivacaine nor in vitro antibacterial activity with ropivacaine and/or bupivacaine [11,14,15], in our study ropivacaine 1% showed antimicrobial activity 3, 12 and 24 h after incubation only at 37ºC and there was a similar antimicrobial activity pattern 24 h after incubation at both 24ºC and 37ºC as well. However, bupivacaine 0.5% inhibted growth of s.aureus at 37ºC only 3 hours after incubation. Notably, levobupivacaine 0.75% showed antimicrobial activity both at 24ºC and 37ºC 12 h after incubation.

When the possible anticandidal effects of bupivacaine and lidocaine were evaluated, 0.15% concentration of bupivacaine inhibited germ tube formation of the candida [16]. In another study lidocaine and bupivacaine at low doses showed fungistatic effect indirectly (yeast metabolic impairment) and at high doses due to direct damage to cytoplasmic membrane [17]. Currently all three LA drugs showed anticandidal effect 3 and 12 hour after incubation without being affected by temperature. However, after 24 hour, 1% of ropivacaine showed an anticandidal effect only at room temperature. The mechanism of reproduction at the 24th hour can be interpreted as improving the tolerance of yeast to the local anesthetic agent. Since this is the case in some antifungal drugs including azole group, where a similar effect was considered. Temporary and reversible local anesthetic effect may have contributed to that effect as well.

In conclusion first of all, the present study has shown the anticandidal effects of levobupivacaine and ropivacaine in addition to bupivacaine. We have also demonstrated possible

antimicrobial (either antibacterial or antifungal) activity of clinically used concentrations of ropivacaine, levobupivacaine and bupivacaine on S. aureus ATCC 6538, S. epidermidis, E.coli and Candida albicans at either room or body temperatures and partly indicated a 12-hour long survivability for antimicrobial effect. Even though not yet known fully, antibacterial and/or antifungal effects of local anesthetics might be promising for potential clinical implications.

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Araştırma Makalesi

Asemptomatik hiperüriseminin hidradenitis süppürativa hastalık seyrine etkileri

Effects of asymptomatic hyperuricemia on the disease course of hidradenitis suppurativa

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Öz

Amaç: Hidradenitis süppürativa (HS) hastaların hayat kalitesini belirgin olarak etkileyen ağrılı abse ve nodüller, sinus traktüsleri ve skarlarla karakterize kronik inflamatuar bir hastalıktır. Hastalığa metabolik sendrom, kardiyovasküler hastalıklar ve artrit gibi komorbiditeler eşlik etmektedir. Asemptomatik hiperüriseminin sıklığı günümüzde giderek artmaktadır ve inflamasyonu şiddetlendirdiğine dair veriler mevcuttur. Bu çalışmada hiperüriseminin HS hastalarında hastalık şiddeti, klinik ve laboratuvar bulgularıyla ilişkisini incelemeyi amaçladık.

Gereç ve Yöntemler: Bu kesitsel çalışmaya Pamukkale Üniversitesi dermatoloji kliniğinde HS tanısı alan hastaların yanı sıra beden kitle indeksi (BKİ), yaş, cinsiyet açısından benzer nitelikte olan, inflamatuar dermatolojik hastalığı olmayan gönüllüler dahil edildi. Serum ürik asit (SÜA), C-reaktif protein (CRP), açlık glukoz, yüksek yoğunluklu lipoprotein kolesterol (HDL), total kolesterol ve trigliserid değerleri kaydedildi. Hastalık şiddetinin belirlenmesi için Hurley sınıflaması ve Uluslararası Hidradenitis Suppurativa Şiddet Skorlaması (IHS4) kullanıldı. Tüm hastalara dermatoloji yaşam kalite indeksi (DYKİ) uygulanarak hastalığın hayat kaliteleri üzerine etkisi incelendi.

Bulgular: Çalışmaya 53 HS tanılı hasta, 44 gönüllü dahil edildi. HS hastalarının 23'ünde (%43.4) hiperürisemi mevcuttu. Hastaların ortalama SÜA seviyeleri, kontrol grubundan yüksek olarak saptandı (6.4±1.4 mg/dL, 4.8±1.4 mg/dL, sırasıyla $p<0.001$). Hiperürisemisi olan hastalarda IHS4 skoru hiperürisemisi olmayan hastalardan belirgin olarak yüksekti (14.8± 12.5 ve 8.5 ±5.6, sırasıyla, $p<0.05$). CRP düzeyleri benzer şekilde hiperürisemisi olan hastalarda daha yüksekti, ancak aralarındaki farklılık istatistiksel açısından anlamlı değildi ($p>0.05$). Hasta grubunda serum CRP düzeyleri ile SÜA seviyeleri arasında pozitif korelasyon vardı ($r=0.342$, $p=0.012$).

Sonuçlar: HS hastalarında asemptomatik hiperürisemi sıklığı artmıştır ve hastalık şiddetiyle ilişkili bulunmuştur. Hiperürisemi, HS ve ilişkili komorbiditeler arasında yakın ilişki bulunmaktadır ve hasta takibinde SÜA düzeyi rutin inceleme arasına alınmalıdır.

Anahtar kelimeler: Hidradenitis süppürativa, ürik asit, asemptomatik hiperürisemi

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Abstract

Aim: Hidradenitis suppurativa (HS) is a chronic inflammatory disease characterized by painful abscesses and nodules, sinus tracts, and scars significantly affecting patients' quality of life. HS is accompanied by comorbidities such as metabolic syndrome, cardiovascular diseases, and arthritis. The frequency of asymptomatic hyperuricemia is increasing nowadays, and it is widely known that it exacerbates inflammation. In this study we aimed to investigate the possible association of hyperuricemia with disease severity, clinical and laboratory findings in HS patients.

Material and Methods: Patients diagnosed with HS at Pamukkale University Dermatology Department were included in this cross-sectional study. Individuals with similar body mass index (BMI), age, and gender, and without inflammatory dermatoses were included in the control group. Serum uric acid (SUA), C-reactive protein (CRP), fasting blood glucose, high-density lipoprotein cholesterol (HDL), total cholesterol, and triglyceride levels were assessed. Hurley classification and International Hidradenitis Suppurativa Severity Score (IHS4) were used to determine disease severity. Dermatology Life Quality Index (DLQI) was used to assess the effect of the disease on their quality of life.

Conclusion: 53 patients with HS and 44 controls were included in the study. Hyperuricemia was present in 23 (43.4%) of HS patients. SUA levels of the patients were higher than the control group (6.4±1.4 mg/dL and 4.8±1.4 mg/dL, respectively, $p<0.001$). The IHS4 score was significantly higher in patients with hyperuricemia than in patients without hyperuricemia. (14.8±12.5 and 8.5±5.6, respectively, $p<0.05$). Serum C-reactive protein (CRP) levels were also higher in patients with hyperuricemia, but the difference was not statistically significant ($p>0.05$). There was a positive correlation between serum CRP levels and SUA levels in the patient group.

Results: The frequency of asymptomatic hyperuricemia is increased in HS patients and is associated with disease severity. There is a close relationship between Hyperuricemia and HS and associated comorbidities, and patients should be evaluated.

Keywords: Hidradenitis suppurativa, uric acid, asymptomatic hyperuricemia

Giriş

Hidradenitis süppürativa aksilla, meme altı, inguinal ve anogenital alanları tutan, tekrarlayıcı nodül, apse ve fistüllerle karakterize kronik, inflamatuvar bir hastalıktır. Uzun dönemde skleroz ve sinüs traktı oluşumuna yol açabilmektedir. HS'nin dünyadaki görülme sıklığının genel popülasyonda %1-4 civarında olduğu belirtilmektedir (1). HS patogenezinde genetik ve çevresel faktörlerin önemli rol oynadığı multifaktöriyel bir hastalıktır. Etiyolojide, mekanik, çevresel ve immünolojik faktörler rol alır (2).

Klinik fenotiplerin çeşitliliği nedeniyle tanı zorlayıcı olabilir. Ortalama olarak, HS hastalarının tanı süresince farklı branşlardan pek çok hekime başvurduğu ve tanının 10 yıl gecikebiliceği bildirilmiştir (1). HS hayat kalitesini olumsuz etkiler ve dünya çapında sosyoekonomik bir yüktür. Hastalığın olası komorbiditelerin yükü hakkında bilgi azdır (3). Uygun taramanın yapılabilmesi için klinisyenlerin bu komorbiditeler hakkında bilgilendirilmesi gerekmektedir. Tedavi stratejileri tasarlanırken mevcut tedavilerin bu komorbiditeleri olumlu ve olumsuz yönde etkileme potansiyeli de dikkate alınmalıdır.

Metabolik sendrom (MS) abdominal obezite, sistemik hipertansiyon, insülin direnci (veya tip 2 diabetes mellitus) ve aterojenik dislipidemiyi içeren bir grup klinik durumu tanımlamak için kullanılan bir terimdir (4). Artmış inflamatuar sitokin aktivitesi ile karakterize protrombotik ve proinflamatuar bir durumdur. Psoriasis, liken planus ve HS gibi inflamatuar deri hastalıkları ile ilişkilendirilmiştir (5). 80 HS hastasının incelendiği hastane bazlı bir çalışmada, metabolik sendrom prevalansı HS'li hastalarda %40 iken, kontrol grubunda ise %13 oranında saptanmıştır (6).

Metabolik sendromla ilişkilendirilmiş komorbiditeler sıklıkla bir aradadır ve bu durum hastalıkların yönetiminde multidispliner yaklaşım gerektirir. Asemptomatik hiperürisemi MS kriterleri arasında olmasa da sıklıkla eşlik eden bir tablodur ve artmış inflamatuar yükle ilişkilendirilmiştir (7, 8). HS patogenezinde önemli rol oynayan interlökin-17 (IL-17) ve tümör nekroz factor (TNF)-α gibi proinflamatuar sitokinler asemptomatik hiperürisemili hastalarda yüksek saptanmıştır (8, 9). HS ile benzer şekilde IL-17 ve TNF-α'nın merkezi rol oynadığı psoriasis ve psoriatik artritte hiperüriseminin hastalık üzerine etkilerini araştıran çok sayıda çalışma vardır (9, 10, 11).

Bununla birlikte HS ve hiperürisemi arasındaki ilişkiye dair literatürde kısıtlı veri bulunmaktadır (12). Bu çalışmada, serum ürik asit düzeylerini etkileyen en önemli faktörlerden biri olduğu için metabolik sendrom varlığını dikkate alarak HS hastalarında hiperürisemi sıklığını ve SÜA düzeylerinin hastalık aktivitesiyle ilişkisini araştırmayı amaçladık.

Gereç ve Yöntemler

Bu tanımlayıcı, kesitsel çalışmaya Pamukkale Tıp Fakültesi Hastanesi Dermatoloji polikliniğine başvuran HS tanılı hastalar dahil edildi. 3 ay içinde sistemik immünsüpresif tedavi ve serum ürik asit düzeyini etkilediği bilinen ilaç kullanan hastalar çalışmaya dahil edilmedi. Kontrol grubu HS hastalarıyla yaş, cinsiyet ve BKİ açısından benzer nitelikte olan ve HS tanısı kendinde ve ailesinde olmayan 18 yaş üstü gönüllüler dahil edildi. Bu çalışma, Helsinki Bildirgesi'ne uygun olarak Pamukkale Üniversitesi Etik Kurulu (No: E-60116787-020-557565) tarafından onaylandı. Bu araştırmada örneklerin kullanılmasından önce hastalardan yazılı bilgilendirilmiş onam alındı.

Hidradenitis süpürativa teşhisi tüm hastalarda fizik muayeneye dayanan morfolojik klinik bulgular ile konuldu. Hastaların yaş ve cinsiyetleri, boy, kilo, bel çevresi, BKİ, sigara kullanım öyküsü, sistemik hastalık öyküsü, aile öyküsü, hastalık başlangıç yaşı, daha önce aldığı tedaviler, hastalık sebebiyle geçirmiş olduğu cerrahi öyküsü, hastalığa eşlik edebilecek komorbiditeler gibi hastalık ile ilgili bilgiler kaydedildi. Hastalığın evrelendirilmesi için Hurley sınıflaması kullanıldı. Bu sınıflamada; evre 1: Sinüs traktı ve skatrizasyon olmaksızın bir ya da daha fazla apse oluşumu, evre 2: Sinüs traktı ve skar oluşumu ile bir veya daha fazla apse formasyonu, evre 3: Hastalıklı bölgede çoklu birbiri ile ilişkili traktların ve apselerin olduğu durumu içermektedir. Hastalık şiddetinin değerlendirilmesi için IHS4 kullanıldı. Tüm hastalara DYKİ uygulanarak hastalığın hayat kaliteleri üzerine etkisi saptanmaya çalışıldı.

Serum ürik asit, CRP, açlık glukoz, HDL kolesterol, total kolesterol, trigliserid ve hemogram ölçümleri kaydedildi. Hiperürisemi, SÜA düzeyinin erkeklerde ≥7 mg/dl, kadınlarda ≥6 mg/dl olması olarak tanımlandı (13).

İstatistiksel Yöntem

İstatistiksel hesaplamalarda istatistik paket programı SPSS (Statistical Package for the Social Sciences Program, v26) programı kullanıldı. Kategorik değişkenler sayı ve oran (%) olarak ve sürekli değişkenler ortalama±standart sapma olarak ifade edildi. Kategorik değişkenleri karşılaştırmak için ki-kare testi kullanıldı. Parametrik verilerin analizi için Student t-testi, non-parametrik verilerin analizi için ise Mann-Whitney U testi kullanıldı. İki sayısal değişken arasındaki doğrusal korelasyon, parametrik test varsayımları karşılandığında Pearson korelasyon analiziyle test edildi ve parametrik test varsayımları karşılanmadığında Spearman korelasyon analizi kullanıldı. $p < 0.05$ değeri istatistiksel olarak anlamlı kabul edildi.

Bulgular

Çalışmaya 53HS tanılı hasta, 44 kendisinde ve ailesinde HS olmayan gönüllü dahil edildi. Hastaların yaş ortalaması 34.2±11.4'idi ve 35'i (%66) erkek 18'i (%34) kadındı. Kontrol grubunun yaş ortalaması 36.4± 11.1'idi ve 26'sı (%59) erkek, 18'i (%41) kadındı. Hasta ve kontrol grubunun demografik, klinik ve labratuvar özellikleri tablo 1'de özetlenmiştir. Hasta ve kontrol grubu arasında yaş, cinsiyet ve BKİ açısından istatistiksel olarak anlamlı fark yoktu.

Tablo 1. Hidradenitis süppürativa hastalarının ve kontrol grubunun demografik, klinik ve laboratuvar özellikleri

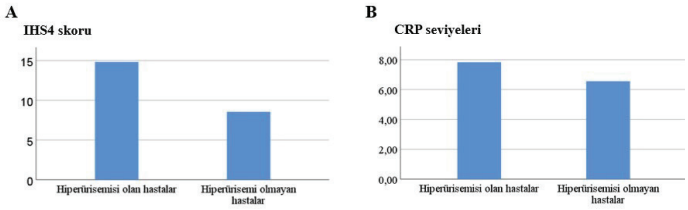
	Hidradenitis süppürativa grubu (n=53)	Kontrol grubu (n=44)	p değeri
Kadın/Erkek	18/35	16/28	p>0.05
Ortalama yaş	34.2±11.49	36. 4± 11.1	p>0.05
Ortalama BKİ	28.6±5.4	27.1±4.3	p>0.05
Ürik Asit (mg/dl)	6.4±1.4	4.8±1.4	p<0.001*
Trigliserid	160.8±102.5	130.1±49.2	p>0.05
Kolesterol	183±40.1	172.8±50.7	p>0.05
Hastalık Süresi (Yıl)	6.3±5.1		
Hiperglisemi n (%)	36 (%67,9)		
CRP seviyesi (mg/dl)	8.2±7.1		
Sigara içiciliği n (%)	39 (%73.5)		
DYKİ	13.1±8.0		
IHS4 skoru	10.5±9.1		

BKİ: Beden kitle indeksi, İHS4: Uluslararası Hidradenitis Suppurativa Skorlaması, CRP: C-reaktif protein, DYKİ: dermatoloji yaşam kalite indeksi

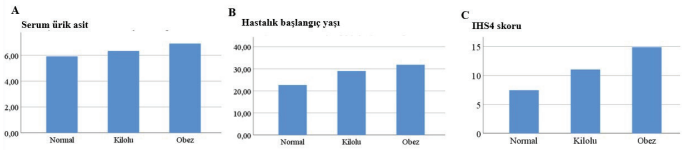
Hastaların ortalama SÜA seviyeleri 6.4±1.4 mg/dL iken kontrol grubunun 4.8±1.4 mg/dL saptandı, bu fark istatistiksek açıdan anlamlıydı (p<0.001). HS hastalarının 23'ünde (%43.4) hiperürisemi mevcuttu. Hiperürisemisi olan hastalarda IHS4 skoru ile belirlenen hastalık aktivitesi seviyeleri hiperürisemisi olmayan hastalardan belirgin olarak yüksekti (sırasıyla, 14.8± 12.5 ve 8.5 ±5.6, p<0.05, Şekil 1A). CRP düzeyleri de benzer şekilde hiperürisemisi olan hastalarda daha yüksekti, ancak fark istatistiksel açısından anlamlı değildi (p>0.05, Şekil 1B). Hasta grubunda serum CRP düzeyleri ile SÜA seviyeleri arasında pozitif korelasyon vardı (r=0.342, p=0.012).

Hastalar göre 25 altında olanlar normal, 25-30 arası kilolu, 30 üzeri obez olarak 3 grubu ayrıldı. Bu sınıflamaya göre SÜA seviyeleri açısından 3 grup arasında istatistiksel anlamlı fark

bulunmadı (Şekil 2A). Bununla birlikte BKİ ile SÜA arasında zayıf da olsa istatistiksel açısından anlamlı olarak pozitif bir korelasyon saptandı (r=0.248, p=0.04) BKİ ile hastalık başlangıç yaşı arasında pozitif korelasyon vardı (r=0.337, p=0.014). BKİ ile hastalık başlangıç yaşı arasındaki ilişki istatistiksel olarak anlamlıydı (p<0.05). BKİ normal olan hastalarda hastalık başlangıç yaşı ortalama 22.6±8.9, kilolu olanlarda 29.1±11.8, obez olanlarda 31.9±7.4 olarak saptandı (p<0.05, Şekil 2B).



Şekil 1. A. Hiperürisemisi olan hastalarda uluslararası hidradenitis süppürativa şiddet skoru (IHS4)**. B.** C-reaktif protein (CRP) düzeyi



Şekil 2. Hastaların beden kitle indeksine göre serum ürik asit (SÜA) düzeyi, hastalık başlangıç yaşı ve İHS4 skorlarının dağılımı.

Hastalık başlangıç yaşı 30 yaş ve üzerinde olanlar geç başlangıçlı, 30 yaş altı erken başlangıçlı olarak başlangıç yaşına göre 2 alt grupta incelendi. Geç başlangıçlı hastalarda ortalama trigliserid düzeyi 218.6±119.20 mg/dl iken erken başlangıçlı hastalarda 122.9±68.6 mg/dl olarak saptandı ve bu fark istatistiksel açıdan anlamlıydı (p<0.01).Hastalık başlangıç yaşı ile, trigliserid (r=0.574, p<0.01) ve kolesterol düzeyleri (r=0.341, p<0.05) arasında pozitif korelasyon saptandı. Erken başlangıçlı hastalarda SÜA seviyeleri (6.7±1.4 mg/dl) geç başlangıçlı hastaların SÜA seviyelerinden (5.8±1.1 mg/dl) belirgin olarak yüksekti (p<0.05). Erken başlangıçlı hastalarda serum CRP seviyeleri (8.2±7.4 mg/dl) geç başlangıçlı hastaların serum CRP seviyelerinden (5.5±4.9 mg/dl) yüksekti, ancak fark istatistiksel açıdan anlamsızdı (p>0.05).

Beden kitle indeksi yüksek hastalarda İHS4 skoru yüksekti ancak bu fark istatistiksel olarak anlamlı değildi (p>0.05, şekil 2C). İHS4 skoruyla hastalık süresi arasında pozitif korelasyon saptandı (r=0.344, p<0.05).

Hastalar Hurley evrelemesine göre kategorize edildiğinde 6 (%11.4) hasta Hurley 1, 23 (%43.4) hasta Hurley 2, 24 (%45.2) hasta Hurley 3 ile uyumluydu. Hurley evrelerine göre hastalar arasında sadece Hurley 2 ve Hurley 3 evreleri arasında hastalık süresi açısından anlamlı farklılık vardı (sırasıyla, 4.1±2.2 yıl, 8.8±7.4 yıl, p<0.05).

Hastalar cinsiyete göre değerlendirildiklerinde erkeklerde İHS4 skoru, serum CRP düzeyleri, BKİ ve SÜA belirgin olarak yüksekti (p<0.05, Tablo 2). Kadın hastalarda DYKİ erkeklere göre yüksek olsa da bu fark istatiksel olarak anlamlı değildi. Kadın hastalarda HDL düzeyleri erkeklere göre belirgin olarak yüksekti (p<0.01, Tablo 2).

Tablo 2. Hidradenitis süppürativa hastalarında cinsiyetin hastalık şiddeti ve laboratuvar bulgularına etkisi

Klinik ve Laboratuvar Özelliği	Kadın (n=18)	Erkek (n=35)	P değeri
İHS4 Skoru	7.1 ± 3.9	12.9 ± 10.5	p =0.012*
CRP düzeyleri	2.9 ± 2.2	9.2 ± 8.3	p =0.001*
BKİ	26.1 ± 4.2	29.8 ± 5.6	p =0.020*
SÜA düzeyleri	5.6 ± 1.2	6.7 ± 1.3	p = 0.007*
DYKİ	13.8± 6.6	12.9 ± 8.8	p >0.05
HDL düzeyleri	54.3 ± 13.2	40.2 ± 10.4	p <0.001*
Trigliserid düzeyleri	132.6 ± 80.3	175.3 ± 110.5	p >0.05
Kolesterol düzeyleri	187.8 ± 33.3	181.0 ± 43.9	p >0.05

BKİ: Beden kitle indeksi, İHS4: Uluslararası Hidradenitis Suppurativa Skorlaması, CRP: C-reaktif protein, SÜA: Serum ürik asit, DYKİ: dermatoloji yaşam kalite indeksi

Tartışma

Bu çalışmanın en önemli bulgularını şöyle sıralayabilir:

(1) HS hastalarında BKİ benzer popülasyona göre SÜA seviyeleri belirgin olarak yüksekti ve SÜA önemli bir inflamasyon belirteci olan serum CRP düzeyleriyle koreleydi.

(2) İleri yaş başlangıçlı hastalarda BKİ ve trigliserid seviyeleri erken yaşta başlayan hastalardan daha yüksek iken SÜA ve CRP seviyeleri düsüktü.

(3) Hem İHS4 skorlaması hem de Hurley evrelemesi hastalık süresiyle pozitif korelasyon göstermekteydi.

(4) Erkek hastalarda inflamatuar belirteçler ve hastalık şiddeti kadın hastalardan belirgin olarak yüksekti.

Ürik asit insan vücudundaki purin katabolik metabolizmasının son ürünüdür Asemptomatik hiperürisemi, ürik asit kristal birikiminin klinik belirtileri olmaksızın serum ürik asit konsantrasyonunun yüksekliği ile karakterizedir. Genel popülasyonda asemptomatik hiperürisemi yaygınlığı yüksektir ve artma eğilimi göstermektedir

(14). SÜA düzeylerinin sağlıklı bireylerde dahi subklinik inflamasyona neden olduğu tespit edilmiştir (15).

Çözünür ürik asidin doğrudan proinflamatuar etkilere sahip olduğunu gösteren pek çok çalışma vardır (16, 17, 18). Ürik asit, hücre dışı ortamda bir antioksidan olmasına rağmen, hücrelerine girdiğinde, kısmen nikotinamid adenin dinükleotid fosfat (NADPH) oksidaz sisteminin aktivasyonu ve mitokondriyal oksidatif stresin uyarılması yoluyla aracılık edilen oksidatif etkilere neden olur (18).

Çözünür ürik asidin endotelyal hücrelerin ve hepatositlerin mitokondrilerinde artmış oksidatif stress inflamazom oluşumuna ve IL-1B, TNF-α ve IL-6 başta olmak üzere inflamatuar sitokinlerin aşırı üretimine yol açarak inflamasyon döngüsüne katkıda bulunur (7, 15).Sistemik inflamasyonun en önemli belirteçlerinden olan CRP ile SÜA arasında çalışmamıza benzer şekilde farklı etnik gruplarda kuvvetli bir korelasyon saptanmıştır (19, 20). Yüksek konsantrasyonlarda SÜA'nın düz kas ve endotel hücre kültürlerinde CRP ekspresyonunu indüklediği tespit edilmiştir.(19).

Beden kitle indeksine göre ayarlanmış kısmi bir korelasyon analizinde SÜA ve CRP seviyelerinin korele olduğu bildirilmiştir. 50.028 Koreli yetişkinin katıldığı popülasyona dayalı kohort çalışmasında, en yüksek başlangıç SÜA seviyelerine sahip bireylerin, takipte en yüksek CRP ortalama değerlerine sahip olduğu SÜA ve CRP arasında doğrusal bir doz-cevap ilişkisi gözlenmiştir(20). Bizim çalışmamızda da hasta grubunda serum CRP düzeyleri ile SÜA seviyeleri arasında pozitif korelasyon vardı. Bu bilgiler ışığında metobolik sendromun eşlik etmediği veya BKİ normal sınırlarda olan HS'li bazı hastalarda görülen asemtomatik hiperüriseminin HS'te görülen sistemik kronik inflamasyon için bir belirteç olabileceğine inanıyoruz.

Yukarıda bahsedildiği gibi HS patogenezinde psoriasisle önemli örtüşme mevcut olup her iki hastalıkta da T yardımcı (Th)1/Th17 yolağı merkezi rol oynar ve iki hastalığın bazı hastalarda birlikte bulunması şaşırtıcı değilidir (9). Psoriazis hastalarında SÜA ile hastalık şiddeti arasındaki korelasyonu inceleyen kesitsel bir çalışmada, psoriasis alan şiddet indeksi hiperürisemik hastalarda normoürisemik hastalara kıyasla yüksek bulunmuştur(21). Yüksek hastalık aktivitesinde artan sistemik inflamasyonun SÜA yüksekliğine katkı sağlayacağını düsündürmektedir. Bu çalışmada da HS şiddeti skorlaması için kullanılan İHS4 skoru hiperürisemili hastalarda daha yüksekti.

Çalışmanın dikkat çekici bulgularından biri ileri yaş başlangıçlı hastalarda BKİ ve trigliserid seviyelerinin daha yüksek olmasıydı. Erken başlangıçlı hastalarda ise SÜA ve serum CRP düzeyleri daha yüksekti. Psoriasis hastalarında fenotiplerine göre hastalık erken başlangıçlı ve geç başlangıçlı olarak 2 alt tipe ayrılmıştır. Tip 1 daha erken başlangıç yaşı ve genetik yatkınlıkta karakterizedir ve hastalık daha şiddetli seyretme eğilimindedir (22). Görebildiğimiz kadarıyla HS için böyle bir fenotiplendirme henüz yapılmamıştır. Hasta sayımız fenotiplerinde yapmak için yetersiz olsa da benzer bir eğilim tespit etmiş olmamızın daha geniş çaplı çalışmalara öncülük edebilmek adına değerli olduğunu düşünüyoruz.

Hidradenitis suppurativa kronik inflamasyonun rol aldığı progresif bir hastalıktır (23). Bununla uyumlu olarak çalışmamızda hastalık süresi uzun hastalarda hem IHS4 skorlarının hem de Hurley evresi daha yüksek olma eğilimindeydi. Hastalık evreleri ilerledikçe fibrosis ve skar gibi geri dönüşümsüz hasarlara yol açacağından zamanında tanı koymak ve progresyonu önlemek kıymetlidir.

Batı ülkelerinde, kadınlarda HS görülme olasılığı erkeklerden daha yüksekken, Doğu ülkelerinde oran tersinedir. Ayrıca, HS'in semptomları erkekler ve kadınlar arasında farklılık gösterir. .Erkeklerde genellikle kalça tutulumu görülürken, kadınlarda aksiller, kasık ve meme altı bölgelerde daha sık tutulum olmaktadır. HS erkeklerde daha şiddetli seyretmektedir (24). Literatürdeki verilerle uyumlu olarak çalışmamızdaki 53 HS tanılı hastanın 35'i (%66) erkek 18'i (%34) kadındı. Ayrıca hastalar cinsiyete göre değerlendirildiklerinde erkeklerde İHS4 skoru, serum CRP düzeyleri, BKİ ve SÜA belirgin olarak daha yüksekti ($p<0.05$).

Sonuç olarak, HS hastalarında ortalama SÜA düzeylerinin kontrol grubuna kıyasla anlamlı derecede yüksek olduğunu gözlemledik. Hiperürisemi, yüksek CRP seviyeleri ve obezitesi olan HS hastalarında yaygındır. Hiperürisemi ve metabolik hastalıkların uygun şekilde kontrol edilmesi, HS sonuçlarını iyileştirmede önleyici bir rol oynayabilir. HS ile hiperürisemi ilişkisini daha derinlemesine incelelemek için gelecekte daha büyük çaplı klinik çalışmalara ihtiyaç vardır.

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ÖSKB ve UB: Çalışmanın konsept ve dizaynlarının oluşturulması, verilerin toplanması, ÖSKB:Verilerin toplanması analizi. ÖSKB ve UB: Makalenin taslağının hazırlanması. ÖSKB ve UB: Makalenin basılmaya hazır son halinin onaylanması.

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Research Article

Effects of left internal mammary artery (LIMA) harvesting during coronary artery by-pass grafting surgery on benign breast diseases

Koroner arter by-pass greftleme ameliyatı sırasında sol internal mamaryen arteri (LIMA) kullanımının benign meme lezyonları üzerine etkileri

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Abstract

Aim: Coronary artery bypass surgery of the primary conduits employed in coronary artery bypass grafting surgery (CABG) is the left internal mammary artery (LIMA), which has garnered considerable attention due to its favorable characteristics and outcomes. There are not enough studies examining the relationship between benign breast diseases (BBD) and LIMA removal. This study is one of the pioneering studies investigating the effects of LIMA removal after bypass surgery in patients with benign breast diseases. This study aims to evaluate the effect of LIMA removal on benign breast diseases in female patients undergoing bypass surgery by analyzing pre- and post-operative breast imaging.

Material and Methods: A total of 47 of 452 female patients who underwent bypass surgery between February 18, 2019, and December 31, 2021, were included in the study. All patients' LIMA were harvested and evaluated, regarding any progression of benign breast diseases.

Results: There was a significant difference between the Breast Imaging Reporting and Data System (BI-RADS) classes of the patients before and after CABG ($p<0.001$). While 40.4% of the patients were BI-RADS class 1 preoperatively, this rate decreased to 14.8% postoperatively. Class 2 level did not show a significant difference, while class 3 level increased from 8.5% to 31.9%. Correlation analysis results between pre-op and post-op BI-RADS classes and age and Body Mass Index (BMI) were analyzed, but no significant correlation value was found. The correlations between pre-op and post-op BI-RADS grades and Hormone Replacement Therapy (HRT) were significant.

Conclusion: It can be concluded that LIMA harvesting during CABG surgery in female patients affects the occurrence of BBD. The change between the pre-op and post-op period was determined by mammography tests. It was shown that there was a significant change in BI-RADS scores on mammography after bypass surgery.

Keywords: Left internal mammary artery, coronary artery bypass grafting, benign breast diseases, BI-RADS, mammography

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Öz

Amaç: Koroner arter bypass cerrahisinde (KABG) olumlu özellikleri ve sonuçları nedeniyle en büyük ilgi gören ve en çok kullanılan graft sol internal mamaryen arterdir. (LIMA). KABG olan hastadalardaki iyi huylu meme hastalıkları (BBD) ile LIMA'nın kullanılması arasındaki ilişkiyi inceleyen yeterli çalışma yoktur. Bu çalışma benign meme hastalıkları olan hastalarda bypass ameliyatı sırasında LIMA çıkarılmasının etkilerini araştıran öncü çalışmalardan biridir. Bu çalışma, bypass ameliyatı geçiren kadın hastalarda ameliyat öncesi ve sonrası meme görüntüleme yöntemlerini analiz ederek LIMA çıkarılmasının iyi huylu meme hastalıkları üzerindeki etkisini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntemler: Çalışmaya 18 Şubat 2019 ile 31 Aralık 2021 tarihleri arasında KABG geçiren 452 kadın hastadan 47'si dahil edildi. Tüm hastalarda LIMA kullanıldı, bu hastalardaki iyi huylu meme hastalıklarının değişimi değerlendirildi.

Bulgular: Hastaların KABG öncesi ve sonrası Meme Görüntüleme Raporlama ve Veri Sistemi (BI-RADS) sınıfları arasında anlamlı fark vardı (p<0,001). Ameliyat öncesi hastaların %40,4'ü BI-RADS sınıf 1 iken ameliyat sonrası bu oran %14,8'e düştü. 2. sınıf düzeyi önemli bir fark göstermezken, 3. sınıf düzeyi %8,5'ten %31,9'a yükseldi. Ameliyat öncesi ve sonrası BI-RADS sınıfları ile yaş ve Beden Kitle İndeksi (BKİ) arasındaki korelasyon analizi sonuçları analiz edildi ancak anlamlı bir korelasyon saptanmadı. Ameliyat öncesi ve sonrası BI-RADS dereceleri ile Hormon Replasman Tedavisi (HRT) arasındaki korelasyonlar anlamlıydı.

Sonuç: Kadın hastalarda KABG ameliyatı sırasında LIMA kullanımının BBD oluşumunu etkilediği sonucuna varılabilir. Mamografi ile takip edilen hastalarda ameliyat öncesi ve sonrası dönem karşılaştırıldığında lezyonlarda değişim olduğunu belirlenedi. Bypass ameliyatı sonrası mamografide BI-RADS skorlarında anlamlı değişiklik olduğu gösterildi.

Anahtar Kelimeler: sol internal mamaryen arter, koroner arter bypass greftleme, benign meme lezyonları, BI-RADS, mamograf

Introduction

CABG remains a cornerstone in the treatment of coronary artery disease, aiming to alleviate angina, improve quality of life, and reduce the risk of myocardial infarction (1–3). Among the various surgical techniques and strategies, the use of grafts plays a crucial role in rerouting blood flow around narrowed or blocked coronary arteries. One of the primary conduits employed in CABG is the LIMA, which has garnered considerable attention due to its favorable characteristics and outcomes (4,5).

Good knowledge of breast anatomy is critical to perform safe breast operations on patients and breast tissue, which consists of only adipose tissue in men and skin, fat, fascia layers, Cooper ligaments, fibroglandular tissue, and lymphatics in women, is located on the chest wall. The internal thoracic artery (internal mammary artery, IMA) is the main arterial perfusion vessel in the breast tissue, where blood vessel density is at its most extreme and perfusion depends on physiologic activity and parenchymal volume, such as during pregnancy or lactation (6). The LIMA emerges from the subclavian artery and descends along the chest wall, running parallel to the sternum. (7,8). Women continue to have greater rates of operative death after coronary artery bypass grafting and a worse long-term prognosis than men. Surgeons are under pressure to determine the optimal surgical approach to enhance the long-term success of coronary bypass grafting for women in light of these findings (9).

BBD includes all non-malignant pathologic conditions of the breast, including proliferative and nonproliferative disorders, associated with infection and inflammation, and often do not carry a progressive malignant condition. Mastitis, abscess, Mondor disease, fat necrosis, breast cysts, duct ectasia, mild hyperplasia, fibroadenoma, sclerosing adenosis, papillomas, and nipple discharge are benign conditions that can develop in women (10,11).

Among women screened for breast cancer, women with prominent mammographic findings, such as architectural distortion, multiple findings, asymmetries, and calcifications, were found to have a higher risk of breast cancer than women with masses; a linear trend between BBD and cancer diagnosis has been reported, with 50% of breast cancers occurring within 5 years of BBD diagnosis (12,13).

The standard technique involves harvesting the LIMA from its origin in the chest wall, preserving its intact pedicle, and minimizing trauma to the arterial wall. Subsequently, the LIMA is anastomosed to the LAD (Left anterior descending) artery beyond the site of stenosis, ensuring optimal blood flow to the jeopardized myocardium (13,14).

It is unclear how arterial revascularization affects long-term outcomes when compared to men. Since the LIMA is the most important artery supplying the breast in women, any traumas in the chest region after bypass grafting surgery may trigger benign breast diseases. Although there have been some

studies on the effect of LIMA on gender-based in-hospital outcomes after bypass graft, the effects of LIMA harvesting on chest diseases have not yet been investigated. Moreover, although there are studies on the status and effect of IMA in patients with breast cancer, there are not enough studies on benign breast diseases (16–19).

This study aims to evaluate the effects of LIMA harvesting on benign breast diseases in female patients undergoing bypass surgery by analyzing preoperative and postoperative breast imaging.

Material and Methods

A total of 452 female patients who underwent CABG operation with harvesting the LIMA at Ankara Bilkent City Hospital Cardiovascular Surgery Clinics between February 18, 2019, and December 31, 2021, were included in the study. However, only 47 of these patients with preoperative and postoperative mammograms were available regarding any progression of benign breast diseases. Power Analysis was applied to determine the number of patients using the Simple Random Sampling method. Power Analysis was performed with GPower 3.1.9.6 (Universitaet Kiel, Germany). "Exact" was selected as the test family and "Proportion: Sign test (Binomial test)" was selected as the analysis. The sample size was calculated as n=38 for a Type-I margin of error of 0.05, power of 95%, estimated odds ratio of p=0.12, and effect size of d=0.10. Accordingly, it was decided that n=47 patients would be sufficient for the study. Ethical approval of the study was obtained from Ankara Bilkent City Hospital Clinical Research Ethics Committee No. 1 with the approval dated 16/08/2022 and numbered E1-23-3684.

A total of 452 female patients who underwent CABG operations in our clinic were included in the study. However, only 47 of these patients with preoperative and postoperative mammograms were available. Power Analysis was applied to determine the number of patients using the Simple Random Sampling method. Power Analysis was performed with GPower 3.1.9.6 (Universitaet Kiel, Germany). "Exact" was selected as the test family and "Proportion: Sign test (Binomial test)" was selected as the analysis. The sample size was calculated as n=38 for a Type-I margin of error of 0.05, power of 95%, estimated odds ratio of p=0.12, and effect size of d=0.10. Accordingly, it was decided that n=47 patients would be sufficient for the study.

Radiological Protocol

Mammography images were assessed as the imaging modality. The presence of mammograms taken one year before and following the procedure was considered to exclude potential confounding factors that may have arisen during the interim period.

After the evaluation, two radiology specialists classified the condition of the breast according to a well-known classification method. This classification called BI-RADS (Breast Imaging Reporting and Data System) is used in breast imaging reports (20).

BIRADS Classification:

Category 0: Additional imaging methods are needed

Category 1: Normal findings

Category 2: Definitely benign findings

Category 3: Probably benign findings

Category 4: Suspicious findings

Category 5: High probability of malignant findings

Category 6: Patients with breast cancer detected by biopsy

Surgical Protocol

The LIMA was prepared as a graft for all patients undergoing coronary artery bypass surgery. Following median sternotomy, the IMA retractor (The original name is IMA Couëtil Sternal Retractor) was positioned, and the left parietal pleura was dissected. The artery was prepared for pedicle use utilizing the LIMA no-touch technique, which involves dissection through the endothoracic fascia. Intercostal arteries are ligated and separated using cautery assistance. The LIMA is dissected from its distal portion, and pulsatile bleeding is assessed. If bleeding exceeds 30 mL/min, the artery is temporarily preserved between the pericardium and the lung with a hot gauze soaked with papaverine, for subsequent use as a graft (Figure 1).

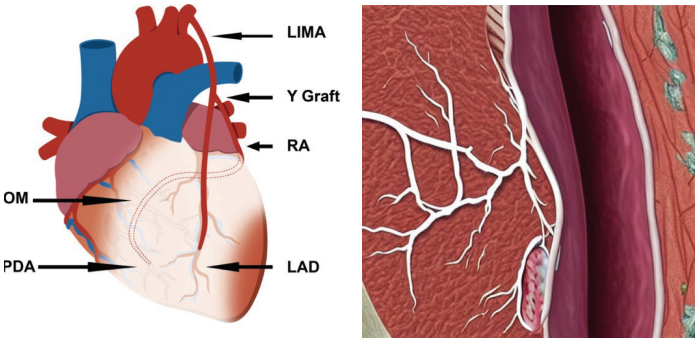

Figure 1. LIMA graft configuration during by-pass surgery

Statistical Analysis

The statistical analyses were performed by SPSS 27.0 (IBM Inc, Armonk, USA) software. The descriptive statistics were presented as mean±SD for numerical variables and frequency (percentage) for categorical variables. Pre-op and post-op BI-RADS scores were

compared with ordinal statistical tests such as the McNmear-Bowker test, Kendall's Tau-b, Somer's d, and Gamma tests. The inter-observer agreement was determined by using Kenall's tau-b and Somer's d also. The p<0.05 was considered as a statistically significant result accepting type-I error as 5%.

Results

A total of 47 patients were included in the study. The mean age of the patients was 58.3±8.2 years. They were generally classified as overweight with a mean Body Mass Index (BMI) of 27.7±3.2 kg/m2. Most of the patients had comorbidities such as Diabetes Mellitus (DM) (70.2%) and Hypertension (HT) (53.1%). Only 17% of the patients had received HRT. The mean length of stay in the intensive care unit was 18.5±28.5 hours and the mean length of hospitalization was 5.7±2.2 days (Table 1).

Table 1. Patient Characteristics and Demographical Data

Total count (n)	47
Age (mean, SD), year	58.3±8.2
BMI (mean, SD), kg/m2	27.7±3.2
HRT (n, %)	8 (17%)
Diabetes Mellitus (n, %)	33 (70.2%)
Hypertension (n, %)	25 (53.1%)
Smoking (n, %)	30 (63.8%)
CABG, anastomosis (mean, SD)	3.4±2.3
CPB time (mean, SD), min	96.5±32.1
Cross-clamp time (mean, SD), min	62.7±28.7
Operation time (mean, SD), min	247.5±104.2
ICU stay (mean, SD), hour	18.5±28.5
Hospital stay (mean, SD), day	5.7±2.2

(BMI: Body Mass Index kg/m2, HRT: Hormone replacement therapy, CABG: Coronary artery bypass grafting, CPB: Cardiopulmonary bypass, ICU: Intensive care unit)

There was a significant difference between the BI-RADS classes of the patients before and after CABG (p<0.001). While 40.4% of the patients were BI-RADS class 1 preoperatively, this rate decreased to 14.8% postoperatively. Class 2 level did not show a significant difference, while class 3 level increased from 8.5% to 31.9% (Table 2) (Figure 2). Correlation analysis results between pre-op and post-op BI-RADS classes and age and BMI were analyzed, but no significant correlation value was found. The correlations between pre-op and post-op BI-RADS grades and HRT were significant. Among the pre-op BI-RADS levels, only level 3 was significantly associated with HRT (p=0.001). All patients at level 3 had received HRT. In post-op BI-RADS levels, levels 2 and 3 were associated with HRT (p<0.001). All patients at level 2 did not receive HRT, while all patients who received HRT were at level 3.

Table 2. Pre-op and post-op BI-RADS classes

	Post-op BI-RADS			
Pre-op BI_RADS	N (%)	N (%)	N (%)	
	1	2	3	Total
1	7 (100.0)	10 (40.0)	2 (13.3)	19 (40.4)
2	0	15 (60.0)	9 (60.0)	24 (51.1)
3	0	0	4 (26.7)	4 (8.5)
Total	7 (14.8)	25 (53.1)	15 (32.1)	47
	Test Statistics	p		
McNemar-Bowker	21.0	<0.001		
Somer's d	0.555	<0.001		
Kendall's Tau-b	0.555	<0.001		
Gamma	0.856	<0.001		

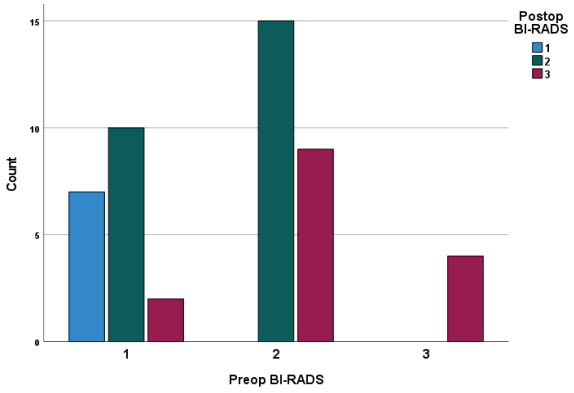

Figure 2. Pre-op and Post-op BI-RADS classification levels

Discussion

Although there are many publications on LIMA removal in the literature on tire and cardiovascular surgery, according to our research, there are not enough studies examining the relationship between benign breast diseases and LIMA removal. This study is one of the pioneering studies investigating the effects of LIMA removal after bypass surgery in patients with benign breast diseases. Therefore, the results of LIMA removal have not been adequately discussed. In our study, there was a significant change in BI-RADS scores on mammography after bypass surgery. BMI values showed that the patients were prone to obesity. The majority had comorbid diseases. LIMA is considered the standard vessel for coronary artery bypass grafting. However, in recent years, numerous studies have demonstrated the importance of LIMA as an endocrine organ with extracellular vesicles known as exosomes in cardiovascular signaling and various pathological conditions (21). BI-RADS levels appear to be associated with HRT uptake. It is not clear how LIMA inference, which is so important, affects outcomes in patients with BBD.

The blood vessel supply to the breast is inferred from branches of the inner thoracic (mammary) course, intercostal supply routes, and the horizontal thoracic course. The venous life systems of the breast parallel the blood vessel life systems within the profound breast tissues, with matched blood vessels and venous branches seen with back intercostal, axillary, and inside thoracic (mammary) vascular pathways. When shallow veins deplete centrally, they more often than not merge on a periareolar circular arrange of veins (circulus venosus of Haller); from this venous plexus, venous blood is channeled into the inside thoracic veins medially and into the sidelong thoracic veins along the side (6).

In a study, it was evaluated IMAs in patients with malignant breast tumors and patients with no breast lesions. The frequencies of IMA anastomoses were not significantly different between patients with and without malignant breast lesions. This phenomenon might also explain contralateral breast metastases that are observed in 10% to 15% of patients 15 years after treatment and even the higher proportion of longer-term survivors (16).

In a case report, it was reported that the left IMA was harvested to create a LIMA bypass graft, resulting in the loss of the perforator branches medially. The lateral thoracic and thoracoacromial arteries, among other axillary branches, are severely attenuated and impacted by extended lengths of calcified atherosclerosis. However, detectable extended stretches of linear calcification traversing the breast tissue provide evidence in favor of small vessel angina. This is thought to have had a part in the necrosis spreading to the right breast's medial side (22).

Although the LIMA graft is most commonly linked to cardiovascular surgery, it has a wide range of applications in plastic surgery in addition to CABG. Plastic surgeons have come to understand the special qualities of LIMA grafts and how they can be used to solve difficult reconstructive problems while also improving aesthetic results and patient satisfaction. The growing significance of LIMA grafts in plastic surgery highlights its ground-breaking uses and revolutionary impact (23). The LIMA transplant is a cornerstone procedure in cardiovascular surgery that provides patients with coronary artery disease (CAD) with hope and healing (24,25).

There are some limitations in our study. First of all, the sample size of the study was small. There were not enough patients with a diagnosis of BBD who needed bypass surgery. Therefore, data were collected to find patients who met the inclusion criteria. Another limitation of the retrospective study is that there were patient files with deficiencies during data analysis and these files could not be included in the study.

In future studies, randomized controlled trials with larger samples will be conducted to reach better levels of evidence.

It can be concluded that the left internal mammary artery graft stands as a paragon of excellence in cardiovascular surgery, embodying the convergence of scientific innovation, surgical skills, and patient-centered care. The utilization of the left internal mammary artery as a graft in coronary artery bypass surgery represents a cornerstone of modern revascularization strategies. Harvesting of LIMA is not a commonly discussed procedure in relation to benign breast diseases. However, in certain cases where there are benign breast conditions like fibroadenomas or benign breast cysts, the BI-RADS scores show that there is a significant change before and after the LIMA harvesting during the bypass surgery.

Conflict of Interest

The authors declare that there is no conflict of interest in this study.

Financial Disclosure

This study was prepared by no means of any funding or grant, and the authors declare that there is no financial disclosure

Author Contribution

Conceptualization: SM

Design: SM

Data collection and processing: SM, ET

Literatur review and Texting: SM, ET

Analysis and Results: SM, ET

Approval: ET

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Research Article

Impact of age on ultrastructural changes in internal thoracic artery in patients undergoing coronary artery bypass grafting

Koroner arter baypas greftleme yapılan hastalarda yaşın internal torasik arterdeki ultrastrüktürel değişiklikler üzerine etkisi

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Abstract

Aim: Age is a known risk factor for cardiovascular disease and plays a role in the atherosclerotic process. The purpose of this study was to look at the impact of aging and associated risk factors on the ultrastructure of internal thoracic arteries in patients undergoing coronary artery bypass grafting.

Material and Methods: We enrolled 27 patients undergoing elective coronary artery bypass grafting at our institute between August-October 2018. Age groups were classified into three: 50-59, 60-69, and 70-79 years. A 2-mm distal portion of the vessel was excised when the ITA was surgically harvested. Transmission electron microscopy was used to investigate the ultrastructural changes. Cell structure, tissue edema, and endothelial mitochondria were all assessed and rated by using semiquantitative analysis.

Results: The ultrastructure of the vessel wall exhibited no significant changes in Group-I. Endothelial wall irregularity with endothelial cells of varying thickness was seen in Group-II. Group-III showed subendothelial edema and localized endothelial wall discontinuity. These changes were particularly severe in the elderly and patients with comorbidities. The greatest permanent cell alterations, such as massive vacuoles and organelle loss, were identified in two patients with kidney failure and hypertension. The average scores assessing the severity of changes in endotohelial cell structure ($P < .001$), tissue edema ($P < .001$), and mitochondria ($P < .001$) were significantly different between groups showing more severe changes with aging.

Conclusions: In elderly patients with comorbidities, the ITA endothelium may exhibit severe ultrastructural alterations, with the most permanent abnormalities reported in those with hypertension and kidney failure. However, The ITA remains the gold standard in CABG with its native resistance to atherosclerosis.

Keywords: Internal thoracic artery, transmission electron microscopy, coronary artery disease, aging

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Öz

Amaç: Yaş, kardiyovasküler hastalık için bilinen bir risk faktörüdür ve aterosklerotik süreçte rol oynar. Bu çalışmanın amacı, koroner arter baypas greftlemesi yapılan hastalarda yaşlanmanın ve ilişkili risk faktörlerinin internal torasik arterlerin altyapısı üzerindeki etkisini incelemektir.

Gereç ve Yöntemler: Ağustos-Ekim 2018 tarihleri arasında birimimizde elektif koroner arter bypass ameliyatı geçiren 27 hasta çalışmaya dahil edildi. Yaş aralıkları 50-59, 60-69 ve 70-79 olmak üzere üç gruba ayrıldı. ITA cerrahi olarak çıkarıldığında damarın 2 mm'lik distal kısmı eksize edildi. Ultrastrüktürel değişiklikleri araştırmak için transmisyon elektron mikroskobu kullanıldı. Hücre yapısı, doku ödemi ve endotelyal mitokondri yarı kantitatif analiz kullanılarak değerlendirildi ve derecelendirildi.

Bulgular: Grup-I'de damar duvarında ultrastrüktürel anlamlı bir değişiklik görülmedi. Grup-II'de değişen kalınlıklarda endotel hücreleri içeren endotel duvar düzensizliği görüldü. Grup-III'de subendotelyal ödem ve lokalize endotel duvar süreksizliği görüldü. Bu değişiklikler özellikle yaşlılarda ve eşlik eden hastalıkları olan hastalarda şiddetliydi. Büyük vakuoller ve organel kaybı gibi en büyük kalıcı hücre değişiklikleri, böbrek yetmezliği ve hipertansiyonu olan iki hastada tespit edildi. Endotelyal hücre yapısındaki (P = 0,001), doku ödemi (P = 0,001) ve mitokondrideki (P = 0,001) değişikliklerin ciddiyetini değerlendiren ortalama puanlar, yaşlanmayla birlikte daha ciddi değişiklikler gösteren gruplar arasında anlamlı derecede farklıydı.

Sonuç: Eşlik eden hastalıkları olan yaşlı hastalarda, ITA endoteli ciddi yapısal değişiklikler sergileyebilir; en kalıcı anormallikler hipertansiyon ve böbrek yetmezliği olanlarda rapor edilmiştir. Ancak ITA, ateroskleroza karşı doğal direnci nedeniyle KABG'de altın standart olmaya devam etmektedir.

Anahtar Kelimeler: İnternal torasik arter, transmisyon electron mikroskobu, koroner arter hastalığı, yaşlanma

Introduction

Due to the aging of the global population, cardiovascular diseases have emerged as prominent causes of mortality on an international scale. Major risk factors include advanced age, diabetes mellitus, hypertension, hyperlipidemia, smoking, and kidney disease [1,2]. Along with these risk factors, clinical implications of inflammation, arterial rigidity, and vascular endothelial dysfunction are significant [3-5].

As numerous observational studies have shown, the left internal thoracic artery (ITA) grafted to the left anterior descending artery (LAD) provides an optimal, reliable conduit. The ITA has demonstrated resistance to atherosclerosis and, when utilized for grafting, decreases the occurrence of significant adverse cardiac events, improves event-free survival, and yields satisfactory graft patency outcomes in comparison to the radial artery or saphenous vein in coronary artery bypass grafting (CABG) [4-6]. Nevertheless, certain histologic studies have identified both early and advanced atherosclerotic lesions, with the intima being the most significantly affected, in ITA grafts from patients with multiple risk factors [7]. Consistent with the steady increase in the life expectancy, our clinical practice increasingly involves frail elderly patients who present with multiple comorbidities and risk factors for CABG [8, 9].

The purpose of this investigation was to determine, through ultrastructural analysis, the impact of aging and associated risk factors on ITA grafts in patients who had undergone CABG.

Material and Methods

Study design and data collection

Twenty-seven patients who underwent elective CABG at our institute between August and October 2018 were included in this study. To facilitate comparison of ultrastructural findings and effective interpretation of the results, the patients were separated into three age groups. Group I included nine patients aged 50-59, Group II included ten patients aged 60-69, and Group III included eight patients aged 70-79 years. Exclusion criteria were; patients with left ventricular ejection fraction less than 40%, age younger than 50 years, ager older than 79 years, patients who underwent emergency CABG, patients who had previously undergone cardiac surgery, patients with severe peripheral vascular disease, and patients which did not receive ITA graft.

Sample collection

ITA harvesting was standardized and protocolized during the study period. After midline sternotomy, the left ITA was harvested as a pedicle using a 20 W monopolar electrosurgical electrode (KLS Martin, Gebrüder Martin GmbH & Co. KG, Tuttlingen, Germany) from its origin at the subclavian artery to its distal bifurcation with the large intercostal branches clipped. Following the administration of systemic unfractionated heparin (300 U/kg), ITA pedicle was treated with topical papaverine to prevent vasospasm, and the graft was seperated from its distal bifurcation site. Tissue samples of approximately two mm were collected from the distal end of the graft. It is known that ITA segments distal to bifurcation are more prone to intimal hyperplasia and atherosclerotic changes. However, we think it is not clinically relevant as these segments are not used in CABG surgery.

Tissue preparation, ultrastructural and semiquantitative analysis

For electron microscopy studies, ITA tissues obtained at the time of CABG was immediately minced into one to two mm pieces and fixed in cold-buffered 2.5% glutaraldehyde solution for 24 hours. A post-fixation procedure was performed in 1% osmium tetroxide solution after the samples were irrigated with Sorenson's Phosphate Buffer (SPB) solution. After the fixation process, samples were irrigated with SPB for the second time and dehydrated with increasing concentrations of alcohol. Samples were then irrigated with propylene oxide and were embedded in the epoxy resin embedding media, and they were left in the incubator for 48 hours. Ultrathin sections, 60nm, were cut with a glass knife on an LKB-Nova Ultramicrotome (Nova, Bromma, Sweden). These ultrathin sections were collected on copper grids, stained with uranyl acetate and lead citrate. The ultrastructural analysis was made with an electron microscope (JEOL JEM EX, Tokyo, Japan) and photographs were obtained. Apart from the morphologic analysis of the tissue samples, slides of each ITA were analyzed with a semiquantitative method by a histopathologist blinded to the study (magnifications 10000×). This scoring method is an original method developed by our histopathologist and several papers have been published by using this methodology [3, 9, 11]. In each artery sample, ten different areas on the slides were evaluated and scored. Endothelial cell structure was scored as follows: 0, normal thickness; 1, decreased thickness of endothelial cells; 2, discontinuities in the endothelial wall; 3, complete damage of endothelial wall. Degree of tissue edema was scored as follows: 0, no edema; 1, edema in the endothelial layer; 2, edema in the endothelium and subendothelium; 3, edema in the endothelium, subendothelium, tunica media, and tunica adventitia. Ultrastructural changes in endothelial mitochondria were scored as follows: 0, normal (ultrastructurally normal mitochondrion); 1, mild (mild degree of swelling, mitochondrion with prominent cristae); 2, moderate (swollen mitochondrion, cloudy swelling); 3, severe (amorphous material deposition in the mitochondrion).

Definitions of Clinical Variables

A resting systolic blood pressure of ≥140 mmHg and a diastolic blood pressure of ≥90 mmHg were considered systemic arterial hypertension, as with a history of high blood pressure or the requirement for antihypertensive treatment. Diabetes mellitus was described as having a diabetes medical history and being currently treated with insulin or oral medicines. A history of dyslipidemia diagnosed and/or treated by a physician was defined as dyslipidemia. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Kidney Disease algorithm to assess kidney function. The greatest serum creatinine level obtained within two days before surgery was used as the preoperative creatinine level [12]. KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (CKD) was used to diagnose and grade the severity of CKD.

Statistical Analysis

Statistical analysis of the data obtained in the study was performed using SPSS statistical software version 26.0 for Windows. Continuous variables are expressed as mean ± SD. A one-way analysis of variance was used to compare the numerical data conforming to a normal distribution after the conformity of numerical data to a normal distribution was evaluated using the Shapiro-Wilk test. The Kruskal-Wallis test was used to compare the numerical data that did not fit a normal distribution. The Pearson chi-square test or Fisher exact test was used to compare categorical data. Statistical significance was set at $P < .05$.

Results

Patient Characteristics

Table 1 shows the demographic data and risk factors of the patients. The mean age of the patients in Group I, II and III were 54.33 ±2.7 years, 63.8 ± 3.5 years, and 72.39 ± 3.1 years, respectively. The mean glycated hemoglobin (HbA1c) level was 8.13% ± 0.7% in Group I, 7.87% ± 0.7% in Group II, and 8.05% ± 0.8% in Group III. The gender distribution, number of patients with hypertension, hyperlipidemia, and history of smoking were not statistically different between groups. There was one male CKD patient in Group II and another

female patient in Group III. eGFR levels and KDIGO CKD grades were 18 (Grade 4) and 14 (Grade 5), respectively.

Table 1. Demographics of patients enrolled in the study.

	Group I (n=9)	Group II (n=10)	Group III (n=8)	p
Age	54.33 ± 2.7	63.8 ± 3.5	72.39 ± 3.1	<0.001
Gender (M/F)	8/1	7/3	4/4	0.253
DM	5	4	2	0.663
HbA1c	8.13 ± 0.7	7.87± 0.7	8.05± 0.8	0.960
Hypertension	2	7	4	0.238
Hyperlipidemia	5	5	1	0.183
Smoking	4	3	2	0.468
CKD	0	1	1	0.723

CKD: Chronic kidney disease; DM: Diabetes Mellitus; F: Female; HbA1c: Glycated hemoglobin; M: male.

The ultrastructural findings

The ultrastructure of the vessel wall was normal in Group I (Figure 1). However, the predominant ultrastructural findings in Group II were irregular endothelium walls with endothelial cells of varying thickness showing heterogeneous pattern (Figure 2). In addition to the alterations seen in Group II, subendothelial edema in focal areas and endothelial wall discontinuity were detected in in Group III (older age group). Diabetes mellitus, hypertension, hyperlipidemia, and renal failure were all evaluated in relation to the ultrastructure of the arterial wall. It was noteworthy to see that severe endothelial and subendothelial ultrastructural alterations were detected in two group III patients with diabetes mellitus and in another patient with DM and HT in group III (Figure 3A). Furthermore, in two patients with CKD from group II and III, irreversible cell deterioration with large vacuoles and reduced organelles in endothelial cells were identified and rated as the most significant permanent abnormalities (Figure 3B).

Semiquantitative Electron Microscopic Scores

Ultrastructural examination of ten different locations on the slides for each artery was undertaken, with scores ranging from 0 to 3. In Group III (older age group, semiquantitative analysis revealed endothelial wall disruption, large vacuoles, reduced organelles, enlarged mitochondria in endothelial cells, and mainly diffuse edema. Group III patients had the highest scores in endothelial cell structure, tissue edema and endothelial mitochondria alterations. Patients in Group II had also higher scores than those in Group I. Average scores assessing the severity of changes in endothelial cell structure (P<.001), tissue edema (P<.001), and endothelial mitochondria (P<.001) were significantly different between groups showing more severe ultrastructural changes with aging (Table 2).

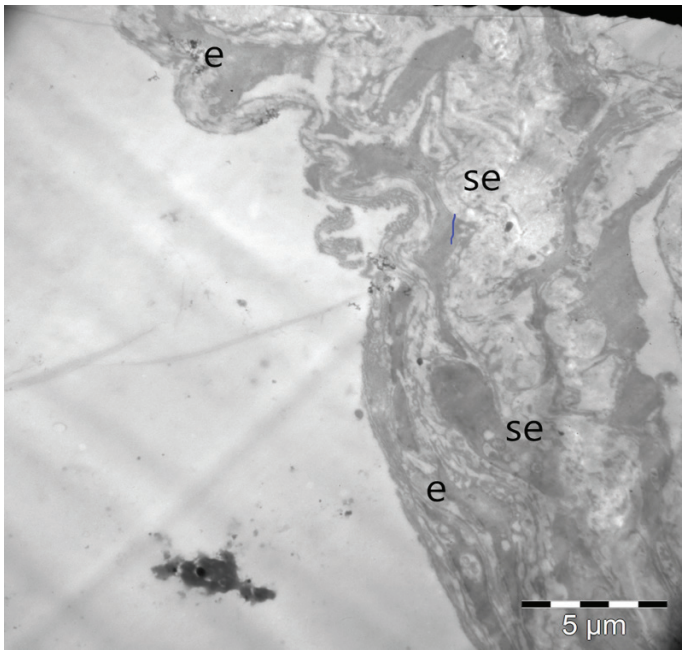

Figure 1. Normal ultrastructural wall appearance in electron microscopy. Electron micrograph of a 57-year-old male patient with no risk factors showing ultrastructurally normal endothelium (e) and subendothelium (se). Original magnification, ×5000.

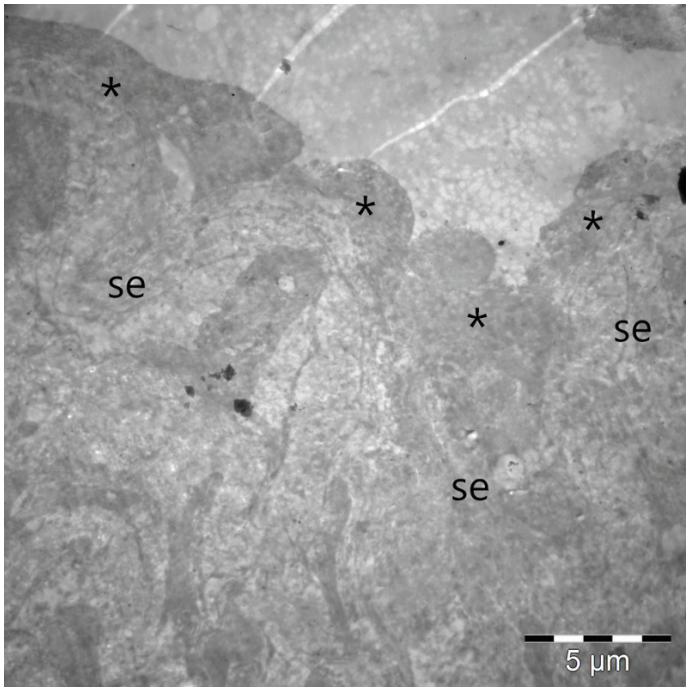

Figure 2. Irregular ultrastructural wall appearance in electron microscopy. Electron micrograph of a 68-year-old female patient with diabetes mellitus and hypertension showing irregular endothelial wall with heterogeneous pattern (*) and ultrastructurally normal subendothelium (se). Original magnification, ×5000.

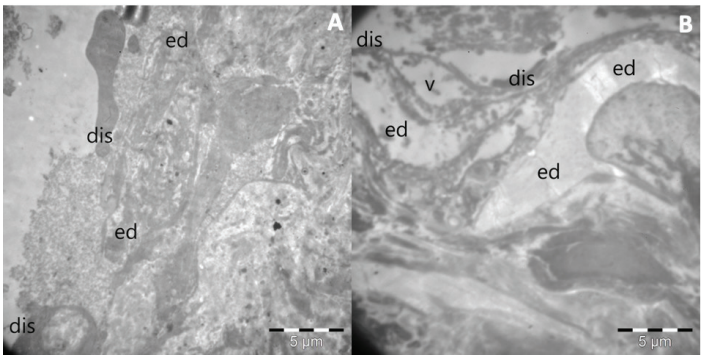

Figure 3. Severe ultrastructural wall alterations in electron microscopy. **(A)** Electron micrograph of a 73-year-old male patient with diabetes mellitus showing subendothelial edema (ed) and discontinuation of endothelial wall (dis). Original magnification, ×5000. **(B)** Electron micrograph of a 72-year-old male patient with chronic kidney disease, hypertension and hyperlipidemia showing subendothelial edema (ed), large vacuoles, and loss of organelles in endothelial cells (v) and discontinuation of endothelial wall (dis). Original magnification, ×5000.

Table 2. Semiquantitative ultrastructural scores.

	Group I (n=9)	Group II (n=10)	Group III (n=8)	p
Endothelial Cell Structure	0.33 ± 0.5	1 ± 0.7	2.13 ± 0.6	<0.001
Degree of Tissue Edema	0.67 ± 0.5	2.3 ± 0.48	2.8 ± 0.46	<0.001
Endothelial Mitochondria	1.78 ± 0.44	2.5 ± 0.53	2.75 ± 0.46	<0.001

Discussion

ITA's histologic and morphologic characteristics make it resistant to atherosclerosis. In the previous three to four decades, ITA grafting has been the gold standard revascularization technique for severe LAD stenoses [8, 13]. When angiography was conducted in symptomatic patients who had previously undergone CABG surgery, observations of blocked ITA graft with patent saphenous vein grafts were quite uncommon in standard surgical practice. Harskamp et al. (2016) discovered an 8.6% ITA failure rate in patients who underwent ITA-LAD revascularization and had angiographic follow-up at 12 to 18 months, with low-grade LAD stenosis, competitive flow, and not having diabetes mellitus being predictors of ITA graft failure [14]. It is also well established that aside from ITA morphology, target vascular region, diameter, and degree of stenosis were critical criteria in determining long-term graft patency in CABG. Despite few research has been published on the ultrastructural abnormalities seen in ITAs, particularly in relation to the clinical profile of the patients, the evidence remained limited.

The predominant ultrastructural findings on transmission electron microscopy examination of the left ITA in this investigation were endothelial wall denudation, endothelial cell irregularity, focal loss of endothelial wall continuity, and subendothelial edema. Large vacuoles and a decreased number of organelles were also identified as permanent alterations in two patients with kidney failure and hypertension. These ultrastructural findings are relevant for patients undergoing CABG surgery as these ultrastructural alterations emphasize the importance of postoperative medical treatment to regulate atherosclerotic process through tight control of modifiable risk factors.

We employed the examination of endothelial integrity, tissue edema, and endothelial mitochondria using a semiquantitative scoring methodology of the specimens, which was similar to prior morphological studies using the same method in the literature [3, 10, 11]. The greatest scores were obtained by two patients who had kidney failure and hypertension. In their histomorphological investigation, Kinoshita et al. (2013) examined ITA specimens from 72 CABG patients and discovered that older age and lower eGFR were independently linked with intimal hyperplasia (odds ratio of 1.90 per 10-year increase) [15]. Ruengsakulrach et al. (1999) evaluated ITA samples from 110 CABG patients and reported that intimal hyperplasia was found in nearly 69% of ITAs, atherosclerotic lesions were found in only 0.7% of ITAs, and plaque formation or medial calcification was not detected [16]. Similarly, in this study, we found a decrease in the thickness of the lining endothelial cells as well as a loss of endothelial wall integrity. However, we did not demonstrate any atherosclerotic changes in the analyzed ITA specimens.

In-vitro techniques have traditionally been employed for histomorphological evaluation of vascular grafts in CABG and cadavers by histology, histochemistry, immunohistochemistry, immunofluorescence, and ultrastructural studies. Borovic et al. (2013) proposed that the ITA is a transitional artery since it lacks a consistent structure and has varying medial content along its length. In their morphometric research, they demonstrated that the slow degeneration of the elastic skeleton developed predominantly with aging, but not with atherosclerosis [17]. Numerous investigations have found that both aging and atherosclerotic diseases reduce the ITA's elastic lamellae thickness while increasing fenestrations. In our study, the severity of the changes increased with age, with the most severe abnormalities found in older patients with hypertension and diabetes. Patients with kidney failure and hypertension have had the most severe and irreversible effects.

Arciniegas et al. (1998) were the first to describe the ultrastructure of atherosclerotic plaques on the ITA [18]. Later, Perrotta et al. (2014) found significant alterations in the walls of two patients' ITA specimens, primarily impacting the intima and media [19.] Furthermore, Bakuy et al. (1998) shown that uncontrolled diabetes mellitus with high HbA1c levels is a strong predictor of ultrastructural histopathological abnormalities such as subendothelial edema and mitochondrial modifications [3]. Ultrastructural alterations and increases in intima-media thickness in ITA samples from CABG patients were highly linked with classic cardiovascular risk factors such age, hypertension, diabetes, and other atypical risk factors like kidney failure [7]. Tyrrell and Goldstein (2020) define the pathophysiology of aging as a complex system including extrinsic and intrinsic vascular variables in their review study. IL-6 signaling and inflammation are induced in the elderly population by myeloid cells that have been exposed to external vascular stimuli. Furthermore, vascular aging worsens the atherosclerotic process, with intrinsic vascular variables significantly impairing mitochondrial function [20].

Comorbidities may worsen the changes seen in senescent cells. For both surgical and interventional revascularization techniques, the best medical therapy and risk factor management may be the sole viable strategies. Current ultrastructural research on ITA specimens on the function of age and comorbidities have significant clinical implications in emphasizing the aim for lowering the burden of these variables in elderly patients undergoing CABG.

There are some potential limitations of the study. Firstly, the concomitant variables that impact ITA morphology might also affect the morphology of target coronaries and aorta. Thus, the degree of ITA morphology does not directly connect to patency rates. Secondly, there is no control group (without coronary disease) for comparison. Finally, due to the lack of clinical follow-up results, we did not extrapolate our histopathological findings to clinical outcomes or graft patency.

In conclusion, while the ITA may experience ultrastructural alterations in elderly patients with comorbidities, it remains the gold standard graft in CABG with its native resistance to atherosclerosis.

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Conflicts of Interest

None.

Competing Interests

The author(s) declare that none

Ethics Committee Approval

This study was approved by the Institutional Review Board of Hacettepe University Hospital (IRB number 16969557-1711), and informed consent was obtained from all participants.

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Research Article

Comparative efficacy of synthetic peptide, platelet-rich plasma, and hyaluronic acid alone or in combination in microfracture treatment of focal chondral defects

Fokal kondral defektlerin mikro kırık tedavisinde sentetik peptit, trombositten zengin plazma ve hyaluronik asidin tek başına veya kombinasyon halinde karşılaştırmalı etkinliği

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ABSTRACT

Aim: Although previous limited studies have evaluated the efficacy of adjuvants used alone or in combination to augment microfracture (MF) treatment for focal chondral defects, there are no studies comparing the outcomes of the synthetic peptide (SP) with other adjuvants such as platelet-rich plasma (PRP), hyaluronic acid (HA), or their combinations. This study aimed to evaluate whether the efficacy of MF treatment in focal chondral defects is influenced by the use of adjuvants either alone or in combination.

Material and Methods: Thirty-six rats were included in the study. Group 1 received MF alone, Group 2 received PRP after MF, Group 3 received HA after MF, Group 4 received a SP after MF, Group 5 received a SP plus PRP therapy after MF, and Group 6 received a SP plus HA therapy. The knees of the rats were assessed according to the International Cartilage Repair Society (ICRS) Cartilage Repair Assessment 1 (ICRS-1) and 2 (ICRS-2).

Results: The median ICRS-1 and ICRS-2 scores in Group 1 were lower compared to the other groups, while these scores in Group 2 and Group 4 were similar and higher than the other groups. Also, these scores in Group 5 and Group 6 were similar and lower compared to Group 3 (Group 1: 1 vs. Group 2: 12 vs. Group 3: 9 vs. Group 4: 11 vs. Group 5: 7 vs. Group 6: 7, $p < 0.001$ for ICRS-1 scores; Group 1: 0 vs. Group 2: 85 vs. Group 3: 70 vs. Group 4: 80 vs. Group 5: 45 vs. Group 6: 45, $p < 0.001$ for ICRS-2 scores).

Conclusion: In the MF treatment of focal chondral defects, SP, PRP, and HA injections have a beneficial adjuvant effect based on macroscopic and histopathological findings. However, the combination of these adjuvants is less beneficial than their individual usage.

Keywords: cartilage defects, hyaluronic acid, microfracture, plasma rich protein, synthetic peptide

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ÖZ

Amaç: Daha önceki sınırlı çalışmalarda, fokal kondral defektlerin mikrokırık (MF) tedavisini güçlendirmek için tek başına veya kombinasyon halinde kullanılan adjuvanların etkinliği değerlendirilmiş olsa da, sentetik peptidin (SP) diğer adjuvanlar olan plazma zengin protein (PRP), hyaluronik asit (HA) ve bunların kombinasyonlarıyla sonuçlarını karşılaştıran bir çalışma bulunmamaktadır. Bu çalışmada fokal kondral defektlerde MF tedavisinin etkinliğinin adjuvanların tek başına veya kombinasyon halinde kullanılmasıyla etkilenip etkilenmediğini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Çalışmaya 36 sıçan dahil edilmiştir. Grup 1'e yalnızca MF uygulandı, Grup 2'ye MF sonrası PRP, Grup 3'e MF sonrası HA, Grup 4'e MF sonrası SP, Grup 5'e MF sonrası SP ve PRP kombinasyonu ve Grup 6'ya MF sonrası SP ve HA kombinasyonu uygulandı. Sıçanların dizleri, Uluslararası Kıkırdak Onarım Derneği (ICRS) Kıkırdak Onarım Değerlendirmesi 1 (ICRS-1) ve 2 (ICRS-2) kriterlerine göre değerlendirildi.

Bulgular: Grup 1'de medyan ICRS-1 ve ICRS-2 skorları diğer gruplara göre daha düşüktü, Grup 2 ve Grup 4'te ise bu skorlar benzer olup diğer gruplara kıyasla daha yüksekti. Ayrıca, Grup 5 ve Grup 6'daki bu skorlar benzerdi, ancak Grup 3'e kıyasla daha düşüktü (ICRS-1 skorları için: Grup 1: 1 vs. Grup 2: 12 vs. Grup 3: 9 vs. Grup 4: 11 vs. Grup 5: 7 vs. Grup 6: 7, $p < 0,001$; ICRS-2 skorları için; Grup 1: 0 vs. Grup 2: 85 vs. Grup 3: 70 vs. Grup 4: 80 vs. Grup 5: 45 vs. Grup 6: 45, $p < 0,001$).

Sonuç: Fokal kondral defektlerin MF tedavisinde SP, PRP ve HA enjeksiyonlarının makroskopik ve histopatolojik bulgulara dayalı olarak yararlı bir adjuvan etkisi vardır. Ancak, bu adjuvanların kombinasyonları, tek başına kullanımlarına göre daha az fayda sağlamaktadır.

Anahtar Kelimeler: hyaluronik asit, mikrokırık, kıkırdak defektleri, plazma zengin protein, sentetik peptit

Introduction

Focal chondral defects of the cartilage are currently an orthopedic problem with increasing incidence in young adults, especially due to the growing tendency to engage in contact sports [1-3]. According to the International Cartilage Repair Society (ICRS) classification, the frequency of grade 3–4 lesions (isolated cartilage lesion requiring repair) is between 16% and 41% [3, 4]. The low healing potential of the cartilage makes treatment very difficult. Treatment modalities vary according to the size of the lesion [5-8]. One of the most frequently used treatment techniques is the microfracture (MF) method, a bone marrow stimulation method which is cost-effective. It can be performed easily in a single session and yields satisfactory outcomes [9, 10]. This method aims to create tissue in the defect site that is closest to normal hyaline cartilage, although the tissue formed is not stable [11-13].

Previous experimental studies have shown that the use of adjuvants may enhance the efficacy of MF treatment, while there is limited research available on this subject [14-16]. These studies have evaluated the efficacy of MF treatment enriched with adjuvants such as platelet-rich plasma (PRP), hyaluronic acid (HA), collagen, and collagen-forming agents, which are believed to have positive effects on cartilage lesion regeneration. A few experimental models compare the individual and combined efficacies of adjuvant therapies in MF treatment with a control group. However, there are no studies comparing the effects of synthetic peptides and their combination forms.

We hypothesized that incorporating synthetic peptide (SP) adjuvant and its combinations into the MF technique could enhance treatment outcomes. Thus, this study aimed to assess the effectiveness of using synthetic peptide, either alone or in combination, in treating cartilage lesions using the MF approach.

Material and Methods

This prospective experimental study was approved by the Acıbadem University Experimental Animal Studies Local Ethics Committee (Jan 16, 2019 No: 2019/02) and was conducted in the research unit and operating rooms of Acıbadem University Experimental Animals Breeding and Research Center. Our study began with 36 experimental animals and was completed with the same number of rats without any loss. The sample size calculated for the study provided a sampling power of 0.90.

Study protocol

The study included 36 Sprague-Dawley female rats weighing 280–330 grams that attained skeletal maturity. The animals were

maintained at a controlled temperature (21°C) and illumination (12-hour day and night cycle) under conventional conditions in standard single cages that restricted their movement. The rats had free access to water and food ad libitum.

The rats were anesthetized by injecting ketamine hydrochloride (Ketalar®, Eczacıbaşı, İstanbul, Turkey) (90 mg/kg) and Xylazine® (Rhompun, Bayer, İstanbul, Turkey) (10 mg/kg) intramuscularly. Cefazolin 20 mg/kg was administered for prophylaxis of surgical site infection. Following skin preparation, the patella was dislocated laterally with medial arthrotomy by making a 2-cm medial parapatellar incision in the right knee region to access the joint. Using the method described by Kawasaki [17] and Yoshoika [18], a full-thickness chondral defect with a width of 1.2 mm and a depth of 1 mm (but not extending into the subchondral region) was created in the femoral medial condyle using a Burr with a diameter of 1.2 mm (Figure 1A-C). After the defects were created, the rats were observed with no additional procedure for 4 weeks to have chronic focal chondral defect. After 4 weeks, the rats were randomly divided into six groups, with six rats in each group. Each rat was kept in a separate cage to prevent carnivorism. The groups started the intervention treatment at the fourth week, and continued until the sixth week. At the end of the 6th week of the treatment rats were sacrified for the evaluation. The groups were organized as follows: Group 1 (control group) was applied MF only; Group 2 received PRP after MF; Group 3 received HA after MF; Group 4 received SP after MF; Group 5 received SP and PRP after MF; Group 6 received SP and HA after MF (Table 1).

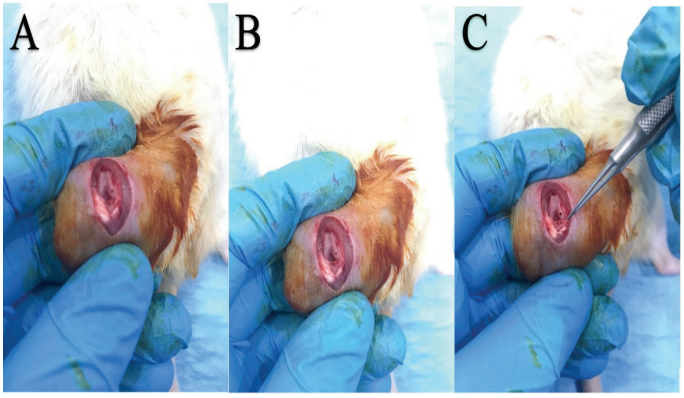

Figure 1. A: Creation of a subchondral defect with a 2-mm Burr in the medial femoral condyle, **B:** The view of the defect in the 4th week, **C:** The image after creating two MF with a 0.6-mm Kirschner wire at the defect.

Table 1. Surgical procedures and adjuvant therapies in the groups

Group	Procedure
1	Two MFs were created with a depth of 2 mm and a diameter of 0.6 mm using a 0.6 mm Kirschner wire (Figure 2)
2	MF + PRP prepared from autologous blood (1 cc) was performed. Half of the 250 µl PRP was injected into the microfracture site and the other half into the knee joint after suturation
3	MF + HA: One half of the 250 µl of HA was injected into the microfracture site, and the other half was injected into the knee joint after suturation
4	MF + SP: One half of the 250 µl SP was injected into the microfracture site, and the other half was injected into the knee joint after suturation.
5	MF + SP + PRP: One half of the 250 µl SP was injected into the microfracture site, and the other half was injected into the knee joint after suturation. Two hours later, 150 µl of PRP prepared from autologous blood was injected into the knee joint.
6	MF + SP + HA: One half of the 250 µl SP was injected into the microfracture site, and the other half was injected into the knee joint after suturation. Two hours later, 150 µl of HA was injected.

HA, hyaluronic acid; MF, microfracture; PRP, platelet-rich plasma; SP, synthetic peptide.

Preparation of adjuvants

PRP was prepared from autologous blood. For this purpose, 1 cc of blood was drawn from each rat. T-Lab tubes containing 3.2% sodium citrate per cubic centimeter were used. A single-motor Electromag centrifuge was utilized to process the blood, with tubes centrifuged at 2,600 rpm for 8 minutes. Approximately 250–300 µl of autologous PRP was obtained from each rat. The mean platelet value in the PRP sample was found to be 16.9 ± 5.6 x 10^3 platelets/µL. Half of the 250 µL of PRP was injected into the MF site, while the other half was injected into the knee joint.

The HA preparation (Altergon TDS) used in the study had a viscosity of 1.5–2.3 m^3/kg and a molecular weight of 1200 KDa. The intra-articular peptide preparation contained collagen tripeptide (IDEA drug).

Post-operative follow-up

No immobilization method was applied to the rats. They were monitored for 6 weeks, provided with comparable environments, nutrition, and care. At the end of this period, the animals were sacrificed using high-dose anesthesia.

Macroscopic and histopathological evaluation

The distal one-third diaphysis of the femur was incised with a saw in the right knee of all groups, and the defected areas were removed for evaluation. Macroscopic evaluation was performed first, using the scoring system of the International Cartilage Repair Society (ICRS-1) [19]. Both ICRS-1 macroscopic cartilage evaluation scores and ICRS-2 histopathological cartilage evaluation scores were applied, which are validated for use in Autologous Chondrocyte Implantation (ACI) and MF [20].

ICRS-1 and ICRS-2 evaluation scores are shown in Tables 2 and 3. The specimens in the groups were evaluated separately by blinded orthopedic surgeon and histopathologist. The main researcher was aware of the rats in the groups while the evaluation. There was a high inter-observer correlation ($r > 0.8$) in ICRS-1 and ICRS-2 scores. ICRS-1 and ICRS-2 were applied to the specimens for macroscopic and microscopic examination, and the average scores of the scientists (orthopedic surgeon and histopathologist) were recorded.

Table 2. Scores of the evoluation system International Cartilage Repair Society Cartilage Repair Assessment-1

Characteristic	Grading	Score
Degree of defect repair	Level of surrounding cartilage	4
	75% repair of defect depth	3
	50% repair	2
	25% repair	1
	0% repair	0
Integration to border zone	Complete integration with border zone	4
	Demarcating border < 1 mm	3
	3/4 of repair tissue integrated, 1/4 with notable border > 1 mm	2
	1/2 of repair integrated with surrounding cartilage, 1/2 with a notable border > 1 mm	1
	From no contact to 1/4 of repair integrated with surrounding cartilage	0
Macroscopic appearance	Intact smooth surface	4
	Fibrillated surface	3
	Small, scattered fissures or cracks	2
	Several, small or few but large fissures	1
	Total degeneration of defect area	0
Total, max		12

The specimens were fixed in 10% formaldehyde for 1 week and decalcified following fixation. Subsequently, they were divided into half longitudinally along the middle-line under the guidance of the defect area and taped for tissue follow-up. The specimens were washed in running water for 3 hours for deacidification. Then, a 13-hour follow-up was performed on an automatic tissue processor (Shanden Exelsior, ES). In this procedure, the tissues were subjected sequentially to formaldehyde twice for 30 minutes, alcohol six times for 60 minutes each, xylene three times for 60 minutes each, and paraffin twice for 60 minutes in the first and 80 minutes in the second cycle. Following tissue processing, 2 µm-thick sections of the paraffin-embedded tissues were stained with Hematoxylin & Eosin, Safranin O, and Toluidine Blue. The sections were evaluated under light microscope (Olympus Bx-50, Olympus Optical). The regenerative tissue thickness on the subcondral bone was measured with an oculometer. Some macroscopic and histopathological specimens of the groups were shown in Figures 2, 3.

Table 3. Scores of the evoluation system International Cartilage Repair Society Cartilage Repair Assessment-2

Histological parameters	Scores
Tissue morphology	0%: full-thickness collagen fibers, 100%: normal cartilage
Matrix staining (metachromasia)	0%: no staining, 100%: full metachromasia
Cell morphology	0%: no round/oval cells, 100%: mostly round/oval cells
Chondrocyte clustering (four or more grouped cells)	0%: present, 100%: absent
Surface architecture	0%: delamination, or major irregularity, 100%: smooth surface
Basal integration	No integration, 100%: complete integration
Formation of a tidemark	0%: no calcification front, 100%: tidemark
Subchondral bone abnormalities/marrow fibrosis	0% abnormal, 100%: normal marrow
Inflammation	0%: present, 100%: absent
Abnormal calcification/ossification	Present, 100%: absent
Vascularization (within the repaired tissue)	Present, 100%: absent
Surface/superficial assessment	0%: total loss or complete disruption, 100%: resembles intact articular cartilage
Mid/deep zone assessment	0%: fibrous tissue, 100%: normal hyaline cartilage
Overall assessment	0%: bad (fibrous tissue), 100%: good (hyaline cartilage)

Statistical analysis

All analyses were conducted using the Number Cruncher Statistical System (NCSS LLC, Utah, USA) software. Descriptive statistical methods (mean, standard deviation, median,

frequency, percentage, minimum, and maximum) were used to evaluate the study data. The suitability of the quantitative data to normal distribution was tested by Shapiro–Wilk test and histograms. Kruskal–Wallis test and Dunn–Bonferroni test were used to compare more than two groups of quantitative variables that did not exhibit normal distribution. P-value < 0.05 was considered statistically significant. The intra-class correlation coefficient was used to evaluate the agreement between the measurements (excellent, r > 0.8; good, r ≤ 0.8; moderate, r ≤ 0.6; fair, r ≤ 0.4; and poor, r ≤ 0.2). The sample size, power level, and effect size were calculated using G * Power Version 3.1.7.

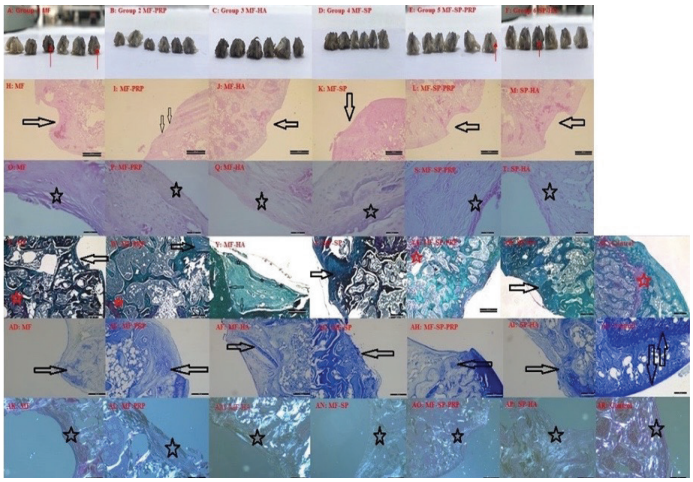

Figure 2. A: Defect area in MF group, **B, C, D:** Macroscopically healed in MF-PRP group, MF-HA group and MF-SP group. E: In MF-SP+PRP group and F: MF-SP+HA groups macroscopically, defect area was shown with arrow in some samples. H: Large defect area in MF Group H&EX40, I: Largely healed defect area in the MF-PRP group H&EX40. J: Partially healed defect area in MF-HA group H&EX40, K: In the MF-SP group, fibrous tissue on the surface and the defect area was healed with new bone formation under it. H&EX40. L: Partially healed defect area in MF-SP+PRP group and M: SP+HA H&EX40. O,S,T: fibrous tissue in MF, MF-SP-PRP and SP-HA groups, hyaline cartilage in P,Q,R:MF+PRP, MF-HA and MF-SP groups, Hematoxylin and Eosin X100. V-AC: Safranin stain appears to stain the growth plate pink (arrow), no surface staining (star) X40: Q: İnitial bone formation at the surface (star) in the SP Group, full integration at the basal (arrow), Safranin OX200. AD-AJ: Positive staining of cartilage surface and newly formed cartilage tissue. Toluidine BlueX100. AK-AR: Polarized light microscopic appearance, collagen fibrils are observed to be light in color.

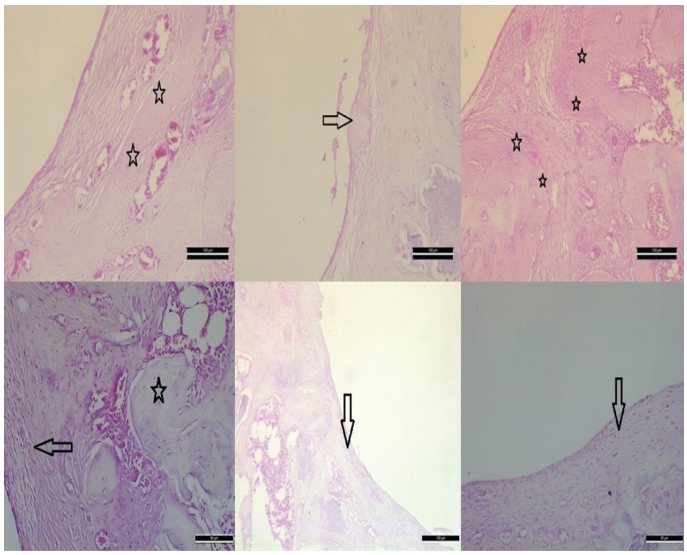

Figure 3. A: Focused view of the initial formation of the hyaline bone in the PRP Group H&EX200, **B:** Hyaline bone formation in the defect area on the surface in the PRP Group H&EX400, **C:** Focused view of new bone formation in SP Group H&EX200, D: Fibrous cartilage (star) and new bone formation (arrow) in Group 5, E: Fibrous cartilage formation on the surface in 5 groups H&EX100. F: Fibrous cartilage close-up view H&EX200

Results

The median ICRS-1 score in Group 1 was lower compared to the other groups, while the median ICRS-1 scores in Group 2 and Group 4 were similar and higher than the other groups. In contrast, the median ICRS-1 scores in Group 5 and Group 6 were similar and lower compared to Group 3 (Group 1: 1 vs. Group 2: 12 vs. Group 3: 9 vs. Group 4: 11 vs. Group 5: 7 vs. Group 6: 7, p < 0.001) (Table 4).

The median ICRS-2 score in Group 1 was found to be lower than in the other groups. In comparison, Group 2 and Group 4 had similar median ICRS-2 scores, which were higher than those in the remaining groups. The median ICRS-2 scores in Group 5 and Group 6 were similar and lower compared to Group 3 (Group 1: 0 vs. Group 2: 85 vs. Group 3: 70 vs. Group 4: 80 vs. Group 5: 45 vs. Group 6: 45, p < 0.001) (Table 5).

The subgroups of ICRS-2 were also compared statistically between the groups. Group 2's tissue morphology score was comparable to that of Group 4, and both groups had higher scores than the other groups. The tissue morphology score of Group 3 was higher compared to Group 5 and Group 6. Group 1 had the lowest score (Group 1: 0 vs. Group 2: 32.5 vs. Group 3: 17.5 vs. Group 4: 27.5 vs. Group 5: 10 vs. Group 6: 10, p < 0.001) (Table 5). While the inflammation scores in Group 2 and Group 4 were similar and lower than in the other groups, no significant differences in inflammation scores were found among the remaining groups (Group 1: 100 vs. Group 2: 55 vs. Group 3: 95 vs. Group 4: 50 vs. Group 5: 100 vs. Group 6: 100, p < 0.001) (Table 5) (Figure 4).

Table 4. Evaluation of the International Cartilage Repair Society Cartilage Repair Assessment-1 (ICRS-1) Scores across the Groups

ICRS-1	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	P-value
Normal, n (%)	0	3 (50.0)	0	2 (33.3)	0	0	0.001*
Close to Normal, n (%)	0	3 (50.0)	6 (100)	4 (66.7)	3 (50.0)	4 (66.7)	
Abnormal, n (%)	6 (100.0)	0	0	0	3 (50.0)	2 (33.3)	
Median (Q1–Q3)	1bcdef (0-2)	12acef (10-12)	9abcef (8-10)	11acef (9-12)	7abcd (6-8)	7abcd (6-8)	0.001*

The data are expressed as median (IQR) or number (%). * P <0.05 shows statistical significance. a: vs. group 1, b: vs. group 2, ac: vs. group 3, d: vs. group 4, e: vs. group 5, f: vs. group 6.

Table 5. Evaluation of the International Cartilage Repair Society Cartilage Repair Assessment-2 (ICRS-2) Scores across the Groups

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	P-value
Tissue morphology (under polarized light)	0^{bcdef} (0-0)	32.5^{acef} (20-35)	17.5^{abef} (10-20)	27.5^{acef} (20-30)	10^{abcd} (5-10)	10^{abcd} (5-10)	0.001 **
Matrix staining (Metacromazia)	0^{bcdef} (0-0)	15^{adef} (10-20)	20^{adef} (10-20)	25^{abc} (20-40)	25^{abc} (20-30)	25^{abc} (20-30)	0.001 **
Cell morphology	0^{bcdef} (0-0)	85^{acef} (70-90)	60^{abdef} (50-70)	75^{acef} (70-80)	42.5^{abcd} (30-50)	37.5^{abcd} (30-50)	0.001 **
Chondrocyte clustering	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	0.999
Surface architecture	0^{bcdef} (0-0)	80^{aef} (70-90)†	70^{aef} (60-70)	75^{aef} (70-90)	25^{abcd} (20-30)	20^{abcd} (20-20)	0.001 **
Basal integration	0^{bcdef} (0-0)	100^{a} (100-100)	100^{a} (100-100)	100^{a} (100-100)	100^{a} (100-100)	100^{a} (100-100)	0.001 **
Formation of a Tidemark	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0.999
Subchondral bone abnormality/bone marrow fibrosis	50^{bef} (40-60)	70^{aef} (50-80)	45^{bef} (30-60)	45^{bef} (40-55)	30^{abcd} (25-40)	30^{abcd} (20-30)	0.001 **
Inflammation	100^{bd} (100-100)	55^{acef} (40-70)	95^{bd} (90-100)	50^{acef} (40-60)	100^{bd} (90-100)	100^{bd} (90-100)	0.001 **
Abnormal calcification/ossification	0^{bcdef} (0-0)	100^{a} (100-100)	100^{a} (100-100)	100^{a} (100-100)	100^{a} (100-100)	100^{a} (100-100)	0.001 **
Vascularization	0^{bcdef} (0-0)	80^{acef} (70-80)	55^{abd} (40-60)	75^{acef} (60-90)	45^{abd} (40-60)	50^{abd} (40-60)	0.001 **
Surface evaluation	0^{bcdef} (0-0)	85^{acef} (80-90)	65^{abdef} (50-80)	85^{acef} (80-90)	50^{abcd} (40-60)	45^{abcd} (40-50)	0.001 **
Deep zone assessment	0^{bcdef} (0-0)	20^{a} (20-30)	17.5^{a} (10-20)	25^{a} (20-30)	15^{a} (10-20)	15^{a} (10-20)	0.001 **
General assessment	0^{bcdef} (0-0)	85^{acef} (80-90)	70^{abdef} (70-80)	80^{acef} (80-90)	45^{abcd} (30-70)	45^{abcd} (30-60)	0.001 **

The data are expressed as median (IQR) or number (%). * P <0.05 shows statistical significance. a: vs. group 1, b: vs. group 2, ac: vs. group 3, d: vs. group 4, e: vs. group 5, f: vs. group 6.

Discussion

This study demonstrated that the use of PRP, SP, and HA alone in the MF treatment of focal chondral defects is more effective compared to the combined adjuvant therapy groups. There are a limited number of studies on the combined use of PRP and MF in osteochondrol defects. In a rat study, Hapa et al. reported that the histopathological outcomes of the MF + PRP Group at 6 weeks were better than those of the MF only group [14]. Using a sheep model with a follow-up duration of 12 months, Milano et al. found that the MF + liquid PRP and MF + gel PRP groups were superior to the MF only group with respect to the integration with the surrounding intact tissue, cartilage thickness, and chondrocyte clustering [21]. Our study found that the MF + PRP treatment group achieved better histopathological scores compared to the other treatment groups.

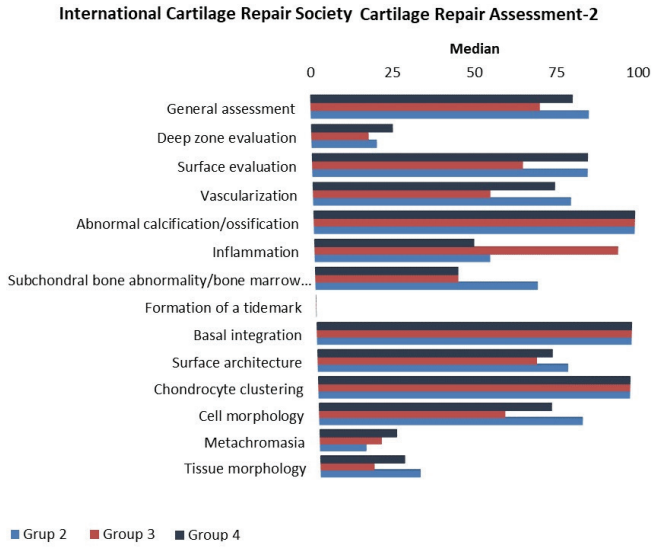

Figure 4: Distribution of the International Cartilage Repair Society Cartilage Repair Assessment-2 Scores across the Group 2, Group 3, and Group 4.

It was determined that intra-articular HA injection prevented cartilage degeneration, decreased synovial inflammation, and increased proteoglycan synthesis [22]. However, the effectiveness of HA in osteoarthritis and the effect of HA injection after MF on the outcomes of the MF technique remain controversial [16, 23-25]. Some studies showed that HA had positive therapeutic effects in the MF treatment of chondral lesions in terms of cartilage regeneration [16, 24]. However, another study demonstrated that the histopathological outcomes of the HA groups in both the early and late periods were not superior to those of the group that received saline injections. In this study, researchers discerned that integration into the surrounding intact cartilage tissue was poor in all groups [25]. In our study, the histopathological scores of the MF + HA treatment group were observed to be higher than those of the MF alone group and the combined treatment groups. Additionally, the ICRS-1 and ICRS-2 scores were similar in the MF + PRP and MF + SP treatment groups but were higher compared to the other groups. In the MF + HA group, these scores were higher than those in the MF-only group and the other combined treatment groups. On the other hand, the tissue morphology scores were higher in the MF + PRP and MF + SP treatment groups than those of the other groups.

In a clinical study, Kesiktaş et al. evaluated 52 patients with osteoarthritis. They divided the patients into HA, PRP, and SP injection groups. During a 3-month follow-up period, they showed a decrease in pain scores and an increase in functional scores in all groups [15]. However, no study evaluating the use of MF augmented with SP in focal chondral defects exists in the literature. The findings of this study not only support the work of Kesiktaş et al., but also show that the ICRS-1, ICRS-2, and tissue morphology scores were higher in the MF + PRP and MF + SP groups.

SP may offer an advantage in clinical practice compared to PRP adjuvant. SP has an advantage in treatment compared to PRP adjuvants. Unlike PRP preparation, it does not require blood collection from the patient or processing under sterile conditions. There are a few studies in the literature evaluating the combined intra-articular use of adjuvant therapies. Researchers have proposed that both adjuvants work through different mechanisms and augment each other's effectiveness in in vitro studies [26, 27]. Naraoka et al. observed that the combined use of SP and HA in the early period of osteoarthritis was more effective than using HA or SP alone and that the combined use increased cell clustering and type II collagen synthesis [28]. However, there are no studies in the literature evaluating the individual and combined use of SP and PRP to augment MF for the treatment of focal chondral defects. The results of our study differ from those in the literature. This study established that the combined use of different adjuvants to augment MF for the treatment of focal chondral defects is more beneficial than MF alone but less effective than the individual use of PRP, HA, and SP. We believe that this finding may be related to the effective dose adjustment.

There were several limitations in our study. First, there are structural differences between rat cartilage and human cartilage, which is a significant limitation. We were unable to enforce an immobilization period for the rats after the MF procedure, which was crucial for effective cartilage treatment. The short follow-up period of the procedure and the use of only female rats were other limitations. However, considering that the cartilage regeneration time of rats is 40–72 days [29-31], and our aim was to compare the efficacy of the adjuvants in augmenting MF for the treatment of focal chondral defects rather than to improve the recovery time, the short follow-up duration was not deemed a significant drawback. Furthermore, our study did not include detailed planning of the dosages of adjuvants and their combinations. In the literature, adjuvants were used at the same dosages in experimental studies [16, 23, 25]. Although the number of rats was limited, power analysis was found to be sufficient. Finally, this study did not evaluate the potential effects of repeated doses of the adjuvants. This could provide more comprehensive insights into the long-term efficacy and safety of these treatments. We believe that

our findings are likely to guide more comprehensive studies in the future. Long-term clinical studies are needed to obtain practicable information.

Conclusion

In the MF treatment of chondral lesions, PRP, SP, and HA injections stimulate regeneration based on the macroscopic and histopathological findings. However, the combined use of these adjuvants is less beneficial than their individual usage.

Funding

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Conflicts of Interest

The authors declare they have no conflicts of interest.

Ethics Approval

The study was approved by the Acıbadem University Experimental Animal Studies Local Ethics Committee (Jan 16, 2019 No: 2019/02).

Availability of Data and Material

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

Authors' contribution

Concept – D.P.K., Design- D.P.K., Data collection and/or processing - D.P.K., E.A., Y.B., A.M., and A.O.A., Analysis and/or interpretation - D.P.K., E.A., Y.B., A.M., and A.O.A., Writing – D.P.K., Critical review- E.A., Y.B., A.M., and A.O.A. All authors read and approved the final version of the manuscript.

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Research Article

The relationship between optic nerve sheath diameter and demographic and clinical findings in patients diagnosed with clinically isolated syndrome

Klinik izole sendromlu hastalarda optik sinir kılıfı çapının demografik ve klinik bulgularla ilişkisi

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Abstract

Aim: This study aimed to assess optic nerve sheath diameter (ONSD) levels in patients diagnosed with clinically isolated syndrome (CIS) who were being followed in the demyelinating diseases clinic, as well as to examine their relationship with demographic characteristics and clinical findings.

Material and Methods: In this cross-sectional prospective study, 14 patients diagnosed with CIS who underwent lumbar puncture for specific cerebrospinal fluid (CSF) analysis were included between January 2024 and August 2024. The ONSD were measured by transorbital sonography. All patients' demographic characteristics, clinical parameters (CSF protein, CSF albumin, serum albumin, immunoglobulin G index, and vitamin D) were recorded.

Results: The patients had a mean age of 39.4 ± 12.8 years, and the majority were women. Oligoclonal bands were positive in all patients. The mean disease duration was 23.5 ± 7.6 days. The ONSD measurements for all patients ranged between 3.1 and 5.9 mm in the sagittal and axial planes of both eyes. There was a strong negative correlation between ONSD levels and age, diseases duration, CSF protein, CSF albumin, serum albumin, and immunoglobulin G index.

Conclusion: This study demonstrated a significant relationship between ONSD and various clinical and laboratory parameters in patients diagnosed with CIS. These findings suggest that ONSD may serve as a valuable, non-invasive marker in assessing disease severity and progression in CIS patients.

Keywords: axonal degeneration, clinically isolated syndrome, demyelinating diseases, multiple sclerosis, optic nerve sheath diameter, transorbital sonography

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Öz

Amaç: Bu çalışma, demiyelinizan hastalıklar polikliniğinde takip edilen ve klinik izole sendrom (KİS) tanısı alan hastalarda optik sinir kılıfı çapı (OSKÇ) seviyelerini değerlendirmeyi ve bu seviyelerin demografik özellikler ve klinik bulgular ile ilişkisini incelemeyi amaçladı.

Gereç ve Yöntemler: Bu kesitsel prospektif çalışmaya, Ocak 2024 ile Ağustos 2024 tarihleri arasında spesifik beyin omurilik sıvısı (BOS) analizi için lomber ponksiyon uygulanan CIS tanısı almış 14 hasta dahil edildi. OSKÇ, transorbital sonografi ile ölçüldü. Tüm hastaların demografik özellikleri, klinik parametreleri (BOS proteini, BOS albümini, serum albümini, immünoglobulin G indeksi ve D vitamini) kaydedildi.

Bulgular: Hastaların ortalama yaşı 39,4 ± 12,8 yıl ve büyük çoğunluğu kadındı. Tüm hastalarda oligoklonal bantlar pozitif saptandı. Ortalama hastalık süresi 23,5 ± 7,6 gündü. Tüm hastalarda OSKÇ ölçümleri, her iki gözde de sagittal ve aksiyel düzlemlerde 3,1 - 5,9 mm arasında idi. OSKÇ ile yaş, hastalık süresi, BOS proteini, BOS albümini, serum albümini ve immünoglobulin G indeksi arasında güçlü bir negatif korelasyon saptandı.

Sonuçlar: Bu çalışma, KİS tanısı almış hastalarda OSKÇ ile çeşitli klinik ve laboratuvar parametreleri arasında anlamlı bir ilişki olduğunu göstermiştir. Bu bulgular, OSKÇ, KİS hastalarında hastalık şiddetini ve ilerlemesini değerlendirmede değerli ve non-invaziv bir biyomarker olarak kullanılabileceğini düşündürmektedir.

Anahtar Kelimeler: aksonal dejenerasyon, klinik izole sendrom, demiyelinizan hastalıklar, multipl skleroz, optik sinir kılıfı çapı, transorbital sonografi

Introduction

Multiple sclerosis (MS) is a chronic disease pathologically characterized by scattered areas of inflammatory demyelination in the central nervous system (CNS) [1]. Over time, 85% of patients who develop MS experience an acute or subacute neurological disorder characterized by a single white matter lesion at clinical onset. This condition is referred to as clinically isolated syndrome (CIS) [2]. In previous studies, the conversion rate from CIS to MS has been reported to vary from 30% to 82% [3].

Axonal and neuronal damage in the CNS plays a crucial role in long-term disability in MS [4]. Recently, there has been a rising interest in cost-effective and accessible biomarkers for detecting this damage [5]. The optic nerve provides a valuable window into these processes, with optical coherence tomography (OCT) offering a precise, non-invasive method to measure retinal nerve fibre layer (RNFL) thickness [6]. A reduction in RNFL thickness has been observed in MS patients, and this has been linked to their level of disability [7]. On the other hand, it has been reported that the optic nerve diameter (OND) or optic nerve sheath diameter (ONSD) measured by ultrasound in MS patients shows a negative correlation with the level of disability and a positive correlation with RNFL thickness and the ganglion cell layer as measured by OCT [8]. Furthermore, it has been shown that there is a high degree of concordance between ultrasonography and magnetic resonance imaging in the measurement of ONSD [9]. However, ONSD and its relationship with clinical parameters in CIS patients have not yet been evaluated.

This study aimed to assess ONSD levels in patients diagnosed with CIS who were being followed in the demyelinating diseases clinic, as well as to examine their relationship with demographic characteristics, clinical and laboratory parameters.

Material and Methods

Following the principles set forth in the Declaration of Helsinki, this prospective study was conducted at the Bakırköy Dr. Sadi Konuk Training and Research Hospital Neurology Clinic from January 2024 to August 2024. The study received approval from the Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (Date: 15/02/2024- No: 2024/02). Informed consent was obtained from all patients prior to their participation in the study.

Study population

A total of 530 patients followed in the demyelinating diseases clinic were evaluated for eligibility according to the research criteria. The study inclusion criteria consisted of patients with a single attack who did not meet the McDonald's 2017 MS diagnostic criteria [10], and those who provided informed consent to participate. The exclusion criteria involved patients younger than 18 or older than 65, pregnant or breastfeeding patients, those who had a new attack and were diagnosed

with MS during follow-up, patients with eye pathologies from trauma or external causes, patients with a diagnosis of vasculitis or additional systemic findings that suggested vasculitis, those suffering from migraine [11], and those with any comorbid conditions. Following the exclusion criteria, 14 diagnosed CIS patients were included in the study.

Study protocol

A detailed physical and neurological examination was performed on the patients included in the study. The demographic, clinical, and imaging data of the patients were obtained at the time of admission. Biochemical parameters were analyzed using venous blood samples collected during outpatient evaluations after a 12-hour fasting period. All samples were analyzed in a single laboratory using the same methodology as described below.

Biochemical analysis

A Beckman Coulter LH 780 device (Mervue, Galway, Ireland) and Hitachi Modular P800 autoanalyzer (Roche Diagnostics Corp., Indianapolis, USA) were used to evaluate patients' venous blood samples. Levels of serum albumin (bromocresol green method) and Vitamin D (enzymatic colorimetric method) were measured.

Ultrasonography evaluation

All measurements were performed using transorbital ultrasonography by a certified neurologist trained in ultrasound, who was blinded to the subjects' clinical data for the duration of the study, in accordance with the ALARA (as low as reasonably achievable) principle. Ultrasonography was performed using the Samsung HM70EVO ultrasound system with a 5-12 MHz linear array B-mode transducer (Samsung Electronics GmBH, Schwalbach, Germany). Subjects were examined in the supine position with the upper part of the body and the head elevated 20º to 30º degrees to avoid any pressure on the eye. They were asked to keep their eyes in a mid-position and to suppress eye movements. For safety, the mechanical index was reduced to 0.2. The probe was placed on the temporal part of the closed upper eyelid using a thick layer of sonography gel. The anterior part of the optic nerve was depicted in an axial plane showing the papillae and the optic nerve in its longitudinal course. The measured parameters were the ONSD, which were measured 3 mm behind the posterior edge of the globe in a horizontal plane.

During the ultrasound examination, the optic nerve is identified by its characteristic appearance. It typically appears as a hyperechoic (bright) tubular structure surrounded by a hypoechoic (dark) rim, which represents the optic nerve sheath (Figure 1). Care is taken to obtain a clear and consistent image of the optic nerve in both transverse (axial) (Figure 1A) and longitudinal (sagittal) (Figure 1B) views. This dual-plane approach helps in ensuring the accuracy and reproducibility of the measurements.

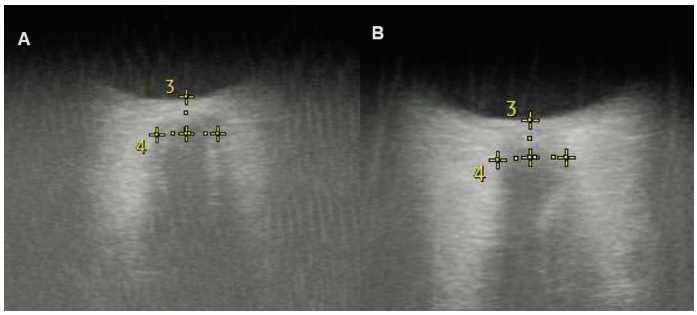

Figure 1. A. Axial plane optic nerve sheath diameter. **B.** Sagittal plane optic nerve sheath diameter

In the longitudinal view, the probe is oriented parallel to the long axis of the optic nerve, providing a sagittal image. In this view, the ONSD is measured at a standardized point, typically 3 mm posterior to the globe, which is considered a reliable site for assessing changes in intracranial pressure (ICP) (Figure 1). This specific measurement point is chosen because it has been shown to correlate well with changes in ICP [11-13].

Once the sagittal view was acquired and the ONSD measurement recorded, the procedure was repeated to capture a transverse (axial) view. In this view, the probe was oriented perpendicular to the long axis of the optic nerve. Measuring ONSD in both the sagittal and axial planes was done to minimize the likelihood of measurement errors and to enhance reliability and accuracy. Moreover, the same measurement procedure was performed on the other eye to ensure the reliability of the data. Bilateral measurements are essential in clinical practice to exclude any asymmetry that might indicate localized pathology. Hence, ONSD measurements were taken from both eyes in both sagittal and axial planes and recorded in millimeters (mm). Each measurement was repeated at least three times, and an average value was calculated to ensure accuracy.

Statistical analysis

All data were analyzed with STATA/MP v.16 software (StataCorp LLC, Texas, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-

Smirnov tests are given as mean ± standard deviation values, while non-normally distributed variables are given as median (25th-75th quartiles) values. Accordingly, Student t-test and Mann-Whitney U test were used for comparisons between two groups. Categorical variables were presented as numbers and percentages, and comparisons between groups were performed using Chi-square and Fisher exact tests. Pearson's and Spearman's correlation analyses were used to assess the associations between numerical variables. Significance was accepted at $P < 0.05$ (*) for all statistical analyses [12-14].

Results

The study included 14 patients, with a mean age of 39.4 ± 12.8 years, most of whom were women. Of the 14 patients, 8 had optic neuritis, 3 has paresthesia, 2 had mono/hemiparesis, and 1 patient was diagnosed with CIS with the clinical presentation of ophthalmoparesis. Oligoclonal bands were positive in all patients. The mean disease duration was 23.5 ± 7.6 days. The demographic and clinical features of the patients are shown in Table 1.

Table 1. Demographic and clinical findings.

Variables	All population n = 14	
	values	range
Demografic findings		
Age, years	39.4 ± 12.8	17 - 60
Gender, n (%)		
Female	9 (64.3)	-
Male	5 (35.7)	-
Smoking, n (%)	2 (14.3)	-
Laboratory findings		
CSF protein, mg/dL	39.1 ± 8.3	22.4 - 53.2
CSF albumin, mg/dL	17.2 ± 4.1	8.9 - 25.5
Serum albumin, mg/dL	38.0 ± 7.0	23.1 - 47.4
Vitamin D	43 (12.5-47.5)	3 - 74
Immunoglobulin G index	1 (0.8-1.2)	0.3 - 1.8
Oligoclonal band, n (%)		
Negative	-	-
Positive	14 (100.0)	-
Diseases duration, days	23.5 ± 7.6	12 - 40

Numerical variables were shown as mean ± SD or median (IQR). Categorical variables were shown as numbers (%). CSF, specific cerebrospinal fluid.

The ONSD measurements for all patients ranged between 3.1 and 5.9 mm in the sagittal and axial planes of both eyes (Figure 2, Table 2). The mean ONSD values were 4.9 ± 0.5 mm for the right sagittal, 4.6 ± 0.6 mm for the right axial, 5.0 ± 0.6 mm for the left sagittal, and 4.8 ± 0.4 mm for the left axial.

There was a strong negative correlation between ONSD levels and age, illness duration, CSF protein, CSF albumin, serum albumin, and immunoglobulin G index (Table 3).

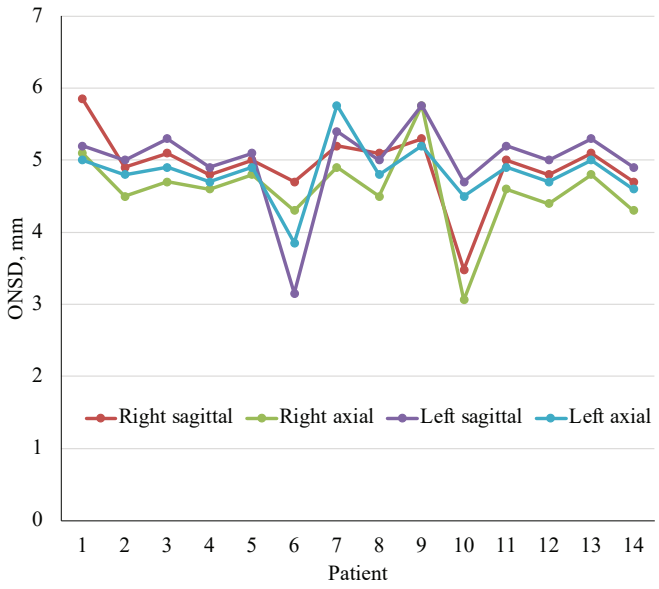

Figure 2. Levels of optic nerve sheath diameter (ONSD) in the patients group

Table 2. Transorbital sonography findings

ONSD, mm	range	mean ± SD	95% CI	median (IQR)
Right sagittal	3.5 - 5.9	4.9 ± 0.5	4.6 - 5.2	5.0 (4.8 - 5.1)
Right axial	3.1 - 5.8	4.6 ± 0.6	4.3 - 4.9	4.6 (4.4 - 4.8)
Left sagittal	3.2 - 5.8	5.0 ± 0.6	4.7 - 5.3	5.1 (4.9 - 5.3)
Left axial	3.9 - 5.8	4.8 ± 0.4	4.6 - 5.1	4.9 (4.7 – 5.0)

CI: confidence interval; IQR, interquartile range; ONSD, optic nerve sheath diameter; SD, standard deviation.

Discussion

To the best of our knowledge, this was the first study to present preliminary findings on the relationship between ONSD and inflammation markers in CIS patients. In CIS patients, ONSD measurements, ranging from 3.1 to 5.9, were negatively correlated with both CSF and serum inflammatory parameters. A strong negative correlation was also observed between ONSD levels and age or illness duration.

The correlation between ONSD measurements and CSF protein and albumin levels suggests that ONSD may serve as a potential marker for increased ICP. Elevated ICP is rarely observed in MS patients due to the inflammatory processes affecting the optic nerve. When ICP increases, it exerts greater pressure on the optic nerve sheath, consequently leading to an increase in the ONSD. This relationship has been supported by various studies indicating that ONSD measurements

Table 3. Relationship between optic nerve sheath diameter and demographic and clinical findings

Variables	Right sagittal		Right axial		Left sagittal		Left axial	
	r	p	r	p	r	p	r	p
Age	-0.895	<0.001*	-0.938	<0.001*	-0.873	<0.001*	-0.926	<0.001*
Gender								
Female	5.0±0.4	0.420	4.6±0.3	0.820	4.9±0.7	0.477	4.8±0.5	0.846
Male	4.8±0.7		4.5±1.0		5.2±0.4		4.9±0.3	
CSF protein	-0.904	<0.001*	-0.923	<0.001*	-0.901	<0.001*	-0.913	<0.001*
CSF albumin	-0.893	<0.001*	-0.923	<0.001*	-0.886	<0.001*	-0.901	<0.001*
Serum albumin	-0.908	<0.001*	-0.914	<0.001*	-0.897	<0.001*	-0.910	<0.001*
Vitamin D	0.257	0.255	0.210	0.314	0.270	0.367	0.246	0.268
Immunoglobulin G index	-0.917	<0.001*	-0.930	<0.001*	-0.870	<0.001*	-0.917	<0.001*
Diseases duration	-0.755	0.002*	-0.791	0.001*	-0.734	0.003*	-0.786	0.001*

CSF, specific cerebrospinal fluid.

can reflect changes in ICP, providing a non-invasive means to monitor this critical parameter in MS patients [15, 16]. Furthermore, it has been documented that the optic nerve sheath thickness can increase in patients experiencing acute optic neuritis, a common manifestation of MS. This condition involves acute inflammation of the optic nerve, which contributes to the thickening of the ONS. However, the sensitivity and specificity of ONSD measurements in detecting acute optic neuritis remain areas of ongoing research and are not yet fully established [17, 18].

In the context of elevated ICP, the expansion of the subarachnoid space surrounding the optic nerve leads to an increased ONSD [19]. This is expected as the increased pressure causes the sheath to distend. However, our study presents an intriguing finding of a negative correlation between ONSD and CSF protein and albumin levels. This finding may suggest that the relationship is more complex, particularly in the chronic stages of the condition. Following acute inflammation, there may be significant axonal damage leading to axonal loss [20]. This neurodegenerative process could result in a subsequent decrease in ONSD over time. The chronic inflammatory state in MS, characterized by ongoing neurodegeneration and axonal loss [21], could thus contribute to a reduced ONSD despite the initial increases associated with acute inflammation. The negative correlation observed in our study may be explained by the chronic stage of disease progression in our patient cohort. In chronic MS, prolonged inflammation and sustained neurodegeneration can lead to the thinning of the ONS due to axonal loss, overshadowing the initial increases in ONSD seen during acute inflammatory episodes [22]. This finding highlights the importance of considering the disease stage when interpreting ONSD measurements in MS patients.

In a study, it was suggested that ONSD measurements could be used as a criterion for temporal dissemination when evaluating MS diagnostic criteria [23]. In our study, the negative correlation between disease duration and ONSD suggests that, given that patients are not in the acute phase, ONSD may decrease due to axonal damage after inflammation. On the other hand, Moreover, the relationship between CSF protein and albumin levels and ONSD suggests that these biomarkers could reflect different aspects of disease pathology. Elevated CSF protein and albumin levels are indicative of blood-brain barrier disruption and inflammation, common features in MS. However, their inverse relationship with ONSD in our study suggests that, in chronic stages, these markers may be more reflective of ongoing neurodegenerative processes rather than acute inflammatory changes. The negative correlation between ONSD measurements and serum albumin levels may be due to the fact that albumin is a major protein in the blood that helps to maintain the integrity of the blood-brain barrier [24]. When albumin levels are low, more fluid and other molecules can leak from the blood vessels into the brain [25], including the ONS. This can lead to an increase in ONSD. The negative correlation between ONSD measurements and the IgG index suggests that ONSD may be a marker of humoral immune response in CIS patients. The IgG index is a measure of the concentration of IgG antibodies which are produced by B cells [26]. An increased IgG index provides insights into disease severity and also the potential for conversion to MS (18) Increased disease severity can lead to axonal damage in the optic nerve [18, 27], which can result in a decrease in ONSD. The negative correlation we observed in our study has suggested that ONSD measurements in CIS patients may provide information about disease severity.

This study has several limitations. First, the sample size was relatively small, with only 14 patients, which may limit the generalizability of our findings. A larger cohort would be needed to confirm the strength and consistency of the observed correlations. Additionally, the cross-sectional design of the study limits our ability to infer causal relationships or track changes in ONSD and inflammatory markers over time. Longitudinal studies are required to evaluate how ONSD evolves with disease progression and its potential role as a predictive marker. Finally, the absence of OCT measurements in our study prevents direct comparison between ONSD and retinal structural changes, which would have provided a more comprehensive view of optic nerve and retinal degeneration.

Conclusion

Our study demonstrated a significant relationship between ONSD and inflammatory markers in patients diagnosed with CIS. ONSD was found to be negatively correlated with CSF and serum parameters of inflammation, suggesting that ONSD may serve as a valuable non-invasive biomarker for assessing neuroinflammation in CIS. These findings provide preliminary evidence that ONSD could be a useful tool in monitoring disease activity and progression in CIS patients. However, further large-scale and longitudinal studies are necessary to validate these findings and explore the combined use of ONSD and OCT in guiding clinical management.

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Conflicts of Interest

The authors declare they have no conflicts of interest.

Ethics Approval

The study was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (Date: 15/02/2024- No: 2024/02).

Availability of Data and Material

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

Authors' contribution

Concept – İ.A., Design – İ.A., Data collection and/or processing – İ.A., B.Y., A.S., and V.Y., Analysis and/or interpretation – İ.A., B.Y., A.S., and V.Y., Literature search – İ.A., B.Y., A.S., and V.Y., Writing – İ.A., Critical review – B.Y., A.S., and V.Y. All authors read and approved the final version of the manuscript.

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Research Article

Effect of probiotic supplementation on hospital admission frequency and inflammatory markers in allergic rhinitis and irritable bowel syndrome patients

Alerjik rinit ve irritabl bağırsak sendromu hastalarında probiyotik takviyesinin hastane yatış sıklığı ve inflamatuar belirteçler üzerine etkisi

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ABSTRACT

Aim: This study aimed to investigate the effect of short-term (3-6 months) probiotic use on patients with recurrent allergic rhinitis (AR) and irritable bowel syndrome (IBS), focusing on changes in inflammation indices and hospital admission frequency.

Material and Methods: This retrospective study included patients diagnosed with IBS and AR between 2020 and 2021, who used probiotic supplements for 3 to 6 months. Clinical data, including demographic characteristics, systemic inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), hemograms before and after probiotic use, and AR-related admission numbers, were collected. The probiotic intervention was compared to a control group receiving standard IBS treatment without probiotics.

Results: Of the 135 patients evaluated, a significant reduction in AR-related hospital admission frequency was observed in the probiotic-treated group compared to the control group ($p<0.001$). Both groups exhibited decreased IBS-related hospital admission frequency, with a higher effect size in the probiotic group (Cohen's d: 1.72 vs 0.55). Probiotic supplementation led to reductions in systemic inflammation indicators (SII, NLR, PLR, CRP) in the treatment group ($p<0.05$), whereas no significant changes were noted in the control group ($p>0.05$).

Conclusion: Probiotic use for at least 3 months in patients with IBS and AR demonstrated improvements in inflammation indices and a reduction in disease-related hospital admission frequency. This suggests a potential role for probiotics in modulating allergic responses and inflammation, providing a promising adjunctive therapy for managing AR, particularly in individuals with co-existing gastrointestinal conditions.

Keywords: probiotics, allergic rhinitis, irritabl bowel syndrome, inflammation indices, disease-releated hospital admission

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ÖZ

Amaç: Bu çalışma, tekrarlayan alerjik rinit (AR) ve irritabl bağırsak sendromu (IBS) olan hastalarda kısa süreli (3-6 ay) probiyotik kullanımının etkisini, özellikle inflamasyon indekslerindeki değişikliklere odaklanarak incelemeyi amaçlamıştır.

Gereç ve Yöntemler: Bu retrospektif çalışmaya 2020-2021 yılları arasında IBS ve AR tanısı almış ve 3-6 ay süreyle probiyotik takviyesi kullanan hastalar dahil edildi. Demografik özellikler, sistemik inflamasyon indeksi (SII), nötrofil-lenfosit oranı (NLR) ve trombosit-lenfosit oranı (PLR) gibi klinik veriler ile probiyotik kullanımı öncesi ve sonrası hemogram sonuçları ve AR ile ilişkili başvuru sayıları toplandı. Probiyotik müdahalesi, probiyotik içermeyen standart IBS tedavisi alan kontrol grubu ile karşılaştırıldı.

Bulgular: Değerlendirilen 135 hasta arasında, probiyotik tedavisi alan grupta kontrol grubuna kıyasla AR ile ilişkili hastane başvuru sıklığında anlamlı bir azalma gözlendi ($p<0.001$). Her iki grupta da IBS ile ilişkili hastane başvuru sıklığında azalma görülürken, probiyotik grubunda daha yüksek bir etki büyüklüğü tespit edildi (Cohen's d: 1.72 vs 0.55). Probiyotik takviyesi, tedavi grubunda sistemik inflamasyon indekslerinde (SII, NLR, PLR, CRP) azalmaya yol açtı ($p<0.05$), ancak kontrol grubunda anlamlı bir değişiklik gözlenmedi ($p>0.05$).

Sonuçlar: IBS ve AR hastalarında en az 3 ay boyunca probiyotik kullanımı, inflamasyon indekslerinde iyileşme ve hastalıkla ilişkili hastane başvuru sıklığında azalma sağladı. Bu, probiyotiklerin alerjik yanıtları ve inflamasyonu modüle etmede potansiyel bir rol oynayabileceğini ve özellikle gastrointestinal bozuklukları olan bireylerde AR yönetimi için umut verici bir yardımcı tedavi olabileceğini göstermektedir.

Anahtar Kelimeler: probiyotikler, alerjik rinit, İrritabl barsak sendromu, inflamasyon indeksleri, hastalığa bağlı hastaneye yatış

Introduction

Evidence indicates that imbalances in the composition of the intestinal microbiota and its interaction with the host may play a role in the development of allergic diseases [1, 2]. While certain bacterial species have been implicated in the onset of asthma and other allergic manifestations, the precise identification of the particular bacteria (or other microbes), their quantities, combinations, and the timing during the gut colonization process that could either prevent or contribute to allergic diseases and asthma remains uncertain [3, 4].

Bacterial colonization, a key determinant of future immunity, is influenced by various factors, notably the mode of childbirth—whether vaginal or cesarean—and the feeding method adopted during the initial months of a child's life [1]. In a comprehensive population-based cohort study, the intake of probiotics during pregnancy was linked to a diminished likelihood of eczema and rhinoconjunctivitis in the child [5]. Previous studies have suggested that a greater diversity in the intestinal microbiota during the initial week of life may correlate with a decreased likelihood of later eczema in infants at elevated risk of allergic disease. Thus, implementing interventions that boost microbial diversity early in life could offer an effective strategy for preventing eczema in high-risk infants [1, 6]. Probiotics may exhibit more promise, albeit with limitations, in preventing allergic diseases rather than treating already-established allergic diseases [7]. Given all of this, there is weak evidence to suggest probiotics in the treatment of allergic disease.

There is growing evidence suggesting potential links between the gastrointestinal and respiratory systems, often referred to as the "gut-lung axis" [8]. There is a higher prevalence of for irritable bowel syndrome (IBS) in individuals with allergic diseases, suggesting a potential link between the two conditions [9, 10]. On the other hand, it has been reported that the risk of developing allergic rhinitis (AR) is higher in patients with IBS compared to those without IBS [11, 12]. This findings suggests that disturbances in gut microbiota can influence systemic immune responses, potentially affecting distant organs such as the respiratory tract. The potential mechanism involves mast cells, which play a role in the pathogenesis of IBS, producing mediators that trigger allergic reactions, and IgE binding to receptors on these mast cells [13]. Atopic patients also exhibit increased intestinal permeability and a higher density of IgE-bearing mast cells compared to non-atopic patients [14]. There is limited evidence suggesting that the gut microbiome of adults with AR may have a reduced diversity and probiotics may have some benefits in the prevention of AR [15-17]. Since both IBS and AR are associated with immune dysregulation and altered microbiota, probiotic supplementation could offer valuable insights into the common mechanisms underlying inflammation and immune responses.

This study aimed to investigate the effect of short-term (3-6 months) probiotic use on patients with recurrent AR and IBS, focusing on changes in basic inflammation indices derived from hemograms during probiotic use and hospital admission frequency.

Material and Methods

This single-center retrospective study was conducted at Gazi Yaşargil Research and Training Hospital between 2020 and 2021. Patients were investigated with ICD code K58 for ISB and J30.9 for AR diagnoses, from the Hospital's software system. Participants who were admitted to the gastroenterology outpatient polyclinic and received a probiotic course as an adjuvant therapy for at least 3-6 months were included in the study and were followed for 2 years. The AR episodes and intensity of anti-allergic drug regimens pre- and post-treatment were compared using the national electronic health tracking system e-Nabiz and the local hospital admissions. A basic flow chart outlining the study design is provided (Figure 1).

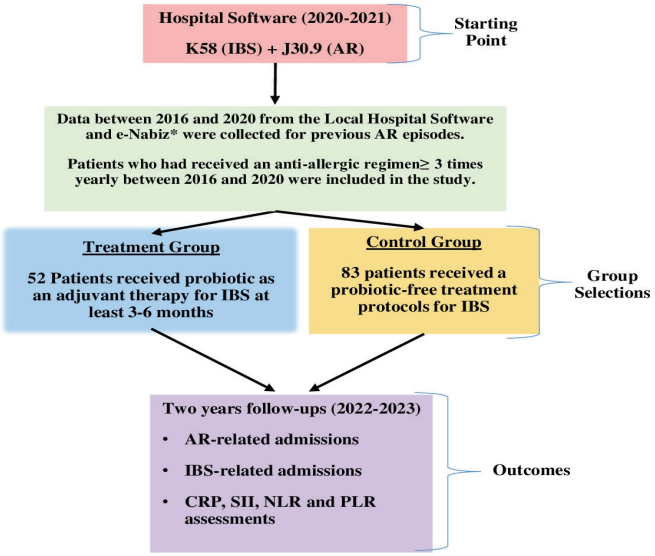

Figure 1. Study design and case selection. K58 and J30.9 (ICD codes for IBS; irritabl bowel syndrome and AR; allergic rhinitis). *e-Nabiz: Turkish Health Ministry National Patient Data Tracking System/registry.

Definitions

IBS: The diagnosis of IBS was based on the Rome IV criteria [18].

Allergic rhinitis: The diagnosis of AR was made based on a comprehensive history and physical examination, considering symptoms such as nasal discharge and congestion, swelling of the eyelids, sneezing, itching in the throat, mouth, and ears, sore throat, dry cough, headache, fatigue, watery and itchy eyes, and partial loss of the sense of smell.

Exclusion criteria

Participants who did not receive a probiotic regimen continuously and properly (cost-related issues, adverse effects, etc.), who received corticosteroids, who were actually under an anti-allergic regimen, or who experienced an acute illness (infectious or inflammatory) were excluded.

Establishing groups

Treatment Group: Patient who received a probiotic containing IBS treatment regimen.

Control Group: Patient who received a probiotic-free IBS treatment regimen.

Data collected

Data on age, gender, body mass index (BMI), C-reactive protein (CRP), complete blood count (CBC), and derived inflammation indices, including the systemic inflammation index (SII), the neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), were documented. Data collection occurred at two time points: initially at the study's commencement and subsequently after at least 24 months of probiotic supplementation in the treatment group. For the control group, data were collected at two points: two years before and two years after inclusion in the study. Probiotics were introduced as an adjunctive therapy for patients with persistent symptoms despite ongoing IBS management. The control group received supplementary pharmacotherapy excluding probiotics.

Calculations

The following formulas were used to calculate the SII, NLR, and PLR:

- SII = (Neutrophil count × Platelet count) / Lymphocyte count
- NLR = Neutrophil count / Lymphocyte count
- PLR = Platelet count / Lymphocyte count

Post-treatment SII, NLR, and PLR were obtained from participants' last hemogram results recorded in the hospital software.

Interventions with probiotics: A commercial product containing 10 billion probiotic organisms was administered daily in one capsule. According to the manufacturer's specifications, each capsule contained 1 billion organisms from the following species: Lactobacillus acidophilus, L. rhamnosus R0011, L. helveticus R0052, L. casei, L. paracasei 1, L. plantarum, L. salivarius, Bifidobacterium lactis, B. breve Br-03, and B. longum BB536. Participants were informed about potential adverse reactions, including abdominal pain, gas, bowel tenderness, diarrhea, and constipation.

IBS treatment: IBS patients received individualized treatment regimens tailored to their specific symptoms, including constipation and diarrhea. These regimens included antispasmodics, loperamide, laxatives, various tricyclic antidepressants, and personalized dietary advice.

Statistical Analysis

Statistical analyses were conducted using appropriate methods to compare demographic and clinical characteristics between the treatment and control groups. Continuous variables were expressed as means ± standard deviations (SD) and compared using independent t-tests or Mann-Whitney U tests, as appropriate. Categorical variables were presented as frequencies and percentages and compared using chi-square tests or Fisher's exact tests. Comparisons of inflammation indices (SII, NLR, PLR, CRP) between pre- and post-treatment periods within each group were conducted using paired t-tests or Wilcoxon signed-rank tests. Differences in AR-related and IBS-related hospital admission frequency between the treatment and control groups were assessed using independent t-tests or Mann-Whitney U tests. Effect sizes were calculated using Cohen's d to evaluate the magnitude of differences between groups. Correlations between inflammation indices and clinical parameters were examined using Pearson or Spearman correlation coefficients, depending on the normality of the data. All statistical tests were two-tailed, and p-values less than 0.05 were considered statistically significant. The analyses were performed using SPSS Version 15.0 for Windows.

Results

A total of 135 eligible patients were evaluated. Female predominance was observed among the participants (n = 91, 67.4%). The clinical and laboratory features of the participants are presented in Table 1. There were significant differences between the treatment and control groups in terms of female gender (98.1% vs. 48.2%, $p < 0.001$) and BMI (23.6 ± 4.3 vs. 25.6 ± 3.0, $p = 0.002$). Allergic rhinitis-related hospital admission frequency significantly decreased in the treatment group ($p < 0.001$), while no significant change was observed in the control group ($p = 0.367$). IBS-related hospital admission frequency decreased in both groups ($p = 0.001$ and $p = 0.021$, respectively) (Table 1). However, the Cohen's d effect size was higher in the treatment group (1.72 vs. 0.55).

Table 1. The clinical and laboratory characteristics of the two groups.

	Treatment Group n = 52	Control Group n = 83	P-value
Age, years	35.8 ± 10.6	38.3 ± 8.8	0.145
Gender, n (%) Male Female	 1 (1.9) 51 (98.1)	 43 (51.8) 40 (48.2)	 <0.001
BMI, kg/m2	23.6 ± 4.3	25.6 ± 3.0	0.002
Mean follow-up, months	17.1 ± 9.2	18.6 ± 7.3	0.133
AR-related hospital admissions frequency	5.1 ± 1.4[a] 2.2 ± 1.3[b]	5.3 ± 1.5[c] 5.2 ± 1.7[d]	a vs. c: 0.496 b vs. d: <0.001 a vs. b: <0.001 c vs. d: 0.367
IBS-related hospital admissions frequency	4.5 ± 1.5[a] 2.3 ± 1.0[b]	4.2 ± 1.5[c] 3.2 ± 1.6[d]	a vs. c: 0.496 b vs. d: <0.004 a vs. b: <0.001 c vs. d: 0.021

Numerical variables were presented as mean ± SD, and categorical variables as numbers (%). a: pre-treatment, b: post-treatment, c: pre-inclusion, and d: post-inclusion. Each superscript is assessed within its line. Abbreviations: BMI, body mass index; AR, allerghic rhinitis; IBS, irritable bowel syndrome.

In the treatment group, SII, NLR, PLR, and CRP levels were significantly reduced ($p < 0.05$), whereas no significant changes were observed in the control group ($p > 0.05$) (Table 2). Pre-treatment SII, NLR, and PLR were correlated with pre-treatment CRP levels in the treatment group ($r = 0.240$, $p = 0.035$; $r = 0.251$, $p = 0.041$; $r = 0.325$, $p = 0.002$, respectively). Age, sex, and BMI had no significant impact on SII, NLR, PLR, or CRP ($p > 0.05$) (Table 2).

According to the records, two patients experienced diarrhea and one patient had abdominal tenderness within the first week of probiotic use. However, the symptoms resolved quickly, and they continued the treatment.

Discussion

Probiotic use has shown benefits for patients with IBS in various clinical studies. However, their efficacy in the treatment of AR remains unclear. This study demonstrated that probiotic supplementation for more than 3 months in patients with both AR and IBS can lead to significant improvements in inflammation indices and reductions in disease-related hospital admission frequency. Our main findings were: (1) Probiotic use was associated with reductions in systemic inflammation markers, including CRP, SII, NLR, and PLR; (2) AR-related hospital admission frequency significantly decreased in the probiotic-treated group compared to the control group; (3) IBS-related hospital admission frequency also decreased in both groups, but the effect was more pronounced in the probiotic group.

Table 2. The comparison of the two groups for inflammation indices

	Treatment Group n = 52	Control Group n = 83	P-value
SII	1685.5 ± 607.9[a] 1452.6 ± 428.9[b]	1434.6 ± 533.9[c] 1458.8 ± 523.8[d]	a vs. c: 0.013 b vs. d: 0.356 a vs. b: 0.036 c vs. d: 0.825
NLR	8.2 ± 1.5[a] 7.2 ± 3.6[b]	7.70 ± 1.8[c] 7.92 ± 2.1[d]	a vs. c: 0.109 b vs. d: 0.035 a vs. b: 0.012 c vs. d: 0.152
PLR	316.5 ± 88.0[a] 279.2 ± 75.6[b]	304.8 ± 101.0[c] 302.9 ± 121.2[d]	a vs. c: 0.480 b vs. d: 0.066 a vs. b: 0.044 c vs. d: 0.911
CRP, mg/dl	1.6 ± 0.8[a] 1.2 ± 0.7[b]	1.35 ± 0.8[c] 1.32 ± 0.8[d]	a vs. c: 0.480 b vs. d: 0.688 a vs. b: 0.028 c vs. d: 0.268

Numerical variables were presented as mean ± SD. a: pre-treatment, b: post-treatment, c: pre-inclusion, and d: post-inclusion. Each superscript is assessed within its line. Abbreviations: SII, systemic inflammation index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelete-to-lymphocyte ratio.

Probiotics are live bacteria that colonize the gastrointestinal tract, exerting beneficial effects on the host's health when administered in adequate amounts [19]. Studies have shown that probiotics can enhance the production of systemic IFN, IL-10, and IL-12, thereby improving the pre-Th1 immune response while reducing Th2 cytokines [20]. Furthermore, Galdeano et al. suggest that the induction of cytokines from activated pro-T-helper type 1 cells, which promote the production of IgG over IgE, can improve the immune-allergic imbalance [19]. Consequently, probiotics have been proposed as modulators of the allergic response and are advocated as therapeutic and preventive interventions for allergic diseases [21, 22].

The rationale for the use of SII, NLR, and PLR in the assessment of various clinical entities is that they demonstrate the relationship between innate and adaptive immunity. AR is related to dysfunction of the acquired immune response, which manifests as oversensitization to allergens [23]. Therefore, changes in these indices can provide affordable, accessible, and objective data for evaluating AR. Several studies have reported that both NLR and PLR are useful markers for diagnosing AR and determining its severity [24, 25]. Our study revealed that SII, NLR, and PLR levels were elevated in individuals with AR and that probiotics could reduce these levels, likely by regulating signaling pathways between immune cells. The reduction in SII, NLR, and PLR is consistent with the observed reduction in CRP among probiotic users, emphasizing the alleviation of immune response. A comprehensive meta-analysis demonstrated significant improvements in most subjective outcomes, including quality of life, total nasal symptom score, total ocular symptom score, and daily total symptom score, following probiotic use in patients with AR [15]. Additionally, no serious adverse effects or cases requiring further intervention were reported after probiotic treatment [26].

Probiotics possess antibacterial, antiviral, and anti-inflammatory properties on mucous membranes, which may help reduce or halt the progression of post-infective IBS [27]. Yoon et al. carried out a randomized, double-blind, placebo-controlled trial to evaluate the effectiveness of multispecies probiotics in IBS patients, using the Rome III criteria. The study included 49 IBS patients, who were randomly assigned to receive either a placebo or multispecies probiotics twice daily for four weeks. By the end of the study, patients in the probiotics group experienced significant improvement in symptoms such as abdominal pain or discomfort, bloating, stool consistency, and frequency [28]. Similarly, previous studies have reported that probiotics reduce pain and symptom severity scores in IBS patients [29-31]. These results demonstrate the beneficial effects of probiotics compared to placebo in IBS management. In this study, both the treatment and control groups exhibited decreased IBS-related hospital admission frequency. However, the reduction was more pronounced in the treatment group, as evidenced by a higher effect size (Cohen's d: 1.72 vs. 0.55). This suggests that probiotic supplementation may lead to a more substantial reduction in the frequency and severity of IBS-related hospital admissions compared to standard IBS treatment without probiotics. Additionally, reductions in systemic inflammation indices (SII, NLR, PLR, and CRP) were observed in the treatment group following probiotic supplementation. This finding suggests that probiotics may exert anti-inflammatory effects, which could be beneficial in managing the inflammatory component of IBS.

This study has several limitations that should be considered. This study has several limitations. First, as a single-center study, the findings may not be generalizable to other populations or clinical settings, and multi-center studies with a more diverse population would improve the external validity. Second, the probiotic product contained multiple bacterial strains, making it difficult to determine the specific

contributions of each strain to the observed effects. Future research could investigate individual strains to clarify their distinct roles. Third, while the two-year follow-up period was adequate for assessing medium-term effects, longer follow-up is needed to evaluate the long-term efficacy and potential relapses. Finally, the study focused on a limited number of inflammatory markers (SII, NLR, PLR, and CRP), and the inclusion of additional immunological markers, such as cytokine levels or gut microbiota composition, could provide a more comprehensive understanding of the probiotic effects on immune modulation and inflammation.

Conclusion

This study highlights the potential benefits of probiotic supplementation in patients with allergic rhinitis and irritable bowel syndrome. The findings suggest that probiotics may contribute to a reduction in disease-related hospital admission frequency and improvements in inflammation indices, indicating a potential role in the management of both allergic and gastrointestinal conditions.

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Conflicts of Interest

The authors declare they have no conflicts of interest.

Ethics Approval

The study was approved by the Gazi Yasargil Training and Research Hospital Clinical Research Ethics Committee (17.11.2023 - No: 567).

Informed Consent

The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

Availability of Data and Material

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

Authors' contribution

Concept – B.H., Design- B.H., Data collection and/or processing - B.H., G.K. and B.E., Analysis and/or interpretation - B.H., G.K. and B.E., Writing – B.H., Critical review- G.K. and B.E., All authors read and approved the final version of the manuscript.

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Araştırma Makalesi

Büyük safen venin çapı ile CEAP skoru arasındaki ilişkinin araştırılması

Investigation of the relationship between the diameter of the greater saphenous vein and ceap score

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Öz

Amaç: Bu prospektif çalışmada, büyük saphenous venin (GSV) farklı seviyelerdeki çapının CEAP skoru, genişlemiş perforatör venlerin tespiti sıklığı ve kronik venöz yetersizlik (CVY) üzerindeki etkilerini araştırdık. Ayrıca, GSV'nin çeşitli seviyelerinde reflü tespiti için eşik değerlerini hesapladık.

Gereç ve Yöntemler: Saphenofemoral kesişim ve diz seviyesindeki büyük saphenous venin çapı ile "c" CEAP skoru, genişlemiş perforatör venlerin prevalansı ve CVY'nin oluşumu gibi çeşitli parametreler arasındaki ilişki Doppler ultrason ile incelendi.

Bulgular: Çalışmaya toplamda 401 hasta dahil edilmiştir. Katılımcıların ortalama yaşı 51,48 ± 25,68 yıldır. GSV çapındaki artış ile saphenofemoral kesişim ve diz seviyesinde reflü varlığında istatistiksel olarak anlamlı bir artış gözlemlendi (p <0,005). Saphenofemoral kesişim için GSV'de 7,85 mm kesme değeri belirlendiğinde, CVY %31,0 duyarlılık ve %84,1 özgüllük ile tespit edilmiştir (AUC (CI): 0,555 (0,442-0,667), p-değeri: 0,343, Youden İndeksi: 0,152). Saphenofemoral kesişim için GSV'de 7,05 mm kesme değeri belirlendiğinde, CVY %34,0 duyarlılık ve %78,1 özgüllük ile tespit edilmiştir (AUC (CI): 0,555 (0,442-0,667), p-değeri: 0,343, Youden İndeksi: 0,124). Diz seviyesinde GSV için 3,95 mm kesme değeri belirlendiğinde, CVY %69,0 duyarlılık ve %75,8 özgüllük ile tespit edilmiştir (AUC (CI): 0,705 (0,601-0,809), p-değeri: 0,001, Youden İndeksi: 0,448). Regresyon analizinde, GSV çapı arttıkça CEAP skorunda anlamlı bir artış gözlemlenmiştir (p <0,001). Saphenofemoral kesişim için GSV'de 7,95 mm kesme değeri belirlendiğinde, ≥4 CEAP puanı (gelişmiş venöz hastalığı gösteren) %92,9 duyarlılık ve %86,3 özgüllük ile tespit edilmiştir (AUC (CI): 0,911 (0,875-0,946), p-değeri: 0,001, Youden İndeksi: 0,792). Diz seviyesinde GSV için 4,45 mm kesme değeri belirlendiğinde, ≥4 CEAP puanı (gelişmiş venöz hastalığı gösteren) %85,7 duyarlılık ve %80,4 özgüllük ile tespit edilmiştir (AUC (CI): 0,916 (0,875-0,956), p-değeri: 0,001, Youden İndeksi0,661).

Sonuç: Sonuç olarak, bu çalışma GSV çapı ile CVY belirtilerinin varlığı arasındaki önemli ilişkiyi ortaya koymuştur. Bulgular, artan GSV çapının yalnızca daha yüksek bir CEAP skoru ile ilişkili olmadığını, aynı zamanda venöz reflü olasılığı ile de korele olduğunu göstermektedir. Diz seviyesindeki GSV çapı ≥3,95 mm olduğunda, CVY olasılığının bir göstergesi olarak tespit edilmektedir. Çap ≥4,45 mm'ye ulaştığında, Doppler ultrason muayenesinin sonunda daha ileri venöz hastalık tespit edilme olasılığı artmaktadır.

Anahtar kelimeler: Venöz yetmezlik, CEAP skoru, vena safena magna

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Abstract

Aim: In this prospective study, we investigated the impacts of the diameter of the great saphenous vein (GSV) at different levels on CEAP scores, the detection frequency of dilated perforator veins, and chronic venous insufficiency (CVI). Additionally, we calculated cutoff values for detecting reflux at various levels of the GSV.

Material and Methods: The relationship between the diameter of the great saphenous vein at the saphenofemoral junction and knee level, and various parameters such as "c" CEAP score, prevalence of dilated perforator veins, and development of CVI were analyzed using Doppler ultrasound.

Results: A total of 401 patients were included in the study, with a mean age of 51.48 ± 25.68 years. A statistically significant increase in the presence of reflux was observed at the saphenofemoral junction and knee level with an increase in GSV diameter ($p < 0.005$). When a cutoff value of 7.85 mm for the GSV at the saphenofemoral junction was determined, CVI was detected with 31.0% sensitivity and 84.1% specificity (AUC (CI): 0.555 (0.442-0.667), p-value: 0.343, Youden Index: 0.152). When a cutoff value of 7.05 mm for the GSV at the saphenofemoral junction was determined, CVI was detected with 34.0% sensitivity and 78.1% specificity (AUC (CI): 0.555 (0.442-0.667), p-value: 0.343, Youden Index: 0.124). A 3.95 mm cutoff value for the GSV at the knee level detected CVI with 69.0% sensitivity and 75.8% specificity (AUC (CI): 0.705 (0.601-0.809), p-value: 0.001, Youden Index: 0.448). Regression analysis showed a significant increase in the CEAP score as the GSV diameter increased ($p < 0.001$). When a cutoff value of 7.95 mm for the GSV at the saphenofemoral junction was determined, a CEAP score of ≥4 (indicating advanced venous disease) was detected with 92.9% sensitivity and 86.3% specificity (AUC (CI): 0.911 (0.875-0.946), p-value: 0.001, Youden Index: 0.792). A 4.45 mm cutoff value for the GSV at the knee level detected a CEAP score of ≥4 with 85.7% sensitivity and 80.4% specificity (AUC (CI): 0.916 (0.875-0.956), p-value: 0.001, Youden Index: 0.661).

Discussion: In conclusion, this study demonstrated a significant relationship between GSV diameter and the presence of CVI symptoms. The findings indicate that increased GSV diameter is associated not only with a higher CEAP score but also with a higher likelihood of venous reflux. When the GSV diameter at the knee level is ≥3.95 mm, it is identified as an indicator of the likelihood of CVI. When the diameter reaches ≥4.45 mm, the probability of detecting more advanced venous disease at the end of a Doppler ultrasound examination increases.

Keywords: Venous insufficiency, CEAP score, great saphenous vein

Giriş

Kronik venöz yetersizlik (KVY), yüzeysel veya derin venlerde kan akışının bozulmasıyla karakterize bir hastalıktır ve venöz hipertansiyona yol açar. KVY, alt ekstremitelerde şişme, cilt değişiklikleri ve rahatsızlık gibi birçok anormal değişikliğin yaşanmasına neden olur; bu durumlar artırılmış venöz basınçtan kaynaklanmaktadır (1). Büyük saphenöz venin (GSV) çapı, KVY değerlendirilmesinde önemli bir gösterge olarak kabul edilmektedir. Venöz reflünün varlığı ile GSV çapı arasındaki ilişki, hastalığın ilerlemesinde kritik bir rol oynayabilir. GSV çapı genellikle KVY mevcut olduğunda genişler (2). Verilerin detaylı bir analizi, çap değişikliklerinin hastalığın ilerlemesi üzerindeki olası etkilerini ortaya çıkarabilir. Klinik, Etiyoloji, Anatomik ve Patofizyoloji (CEAP) skoru, kronik venöz hastalığın klinik, etyolojik, anatomik ve patofizyolojik bileşenlerini değerlendiren bir sınıflama sistemidir (3). Bu çalışmada, büyük saphenöz venin çeşitli seviyelerdeki çapının CEAP skorunu, perforatör venlerin sıklığını ve KVY oluşumunu nasıl etkilediğini araştırdık. Ayrıca, GSV'deki reflü tespiti için eşik değerleri hesapladık.

Gereç ve Yöntemler

Hasta Seçimi ve Çalışma Tasarımı

Bu araştırma, Mart 2023 ile Temmuz 2024 tarihleri arasında, yerel araştırma etik komitesinin onayı ile kurumumuzda gerçekleştirilmiştir. Tüm katılımcılardan yazılı bilgilendirilmiş onam alınmıştır. Doppler ultrason alanında 8 yıllık deneyime sahip bir radyolog (F.Z.A.) tarafından, Hitachi Sağlık Makinesi kullanılarak yüksek frekanslı (6-12 MHz) lineer dizi prob ile tüm alt ekstremite Doppler ultrason muayeneleri yapılmıştır. Çalışmadan dışlanan hastalar arasında tromboflebitis veya akut derin ven trombozu bulunanlar, Valsalva manevrasını yapamayan hastalar ve KVY tedavisi geçmişi olan hastalar yer almaktadır. Çalışmaya sonuçta 401 kronik bacak ağrısı olan hasta dahil edilmiştir. Semptomatik hastalar, bacak ağrısı, kramplar, ülserler, kaşıntı, bacak veya ayak bileği şişmesi (ödem), lipodermatoskleroz, cilt atrofisi, cilt kalınlaşması ve ayak bilekleri etrafında cilt rengi değişiklikleri (pigmentasyon, egzama) gibi çeşitli venöz yetersizlik semptomları göstermekteydi, ayrıca görünebilir varisli damarlar da mevcuttu.

Hasta grubu, CEAP sınıflama sistemi kullanılarak kronik venöz bozukluklar açısından kategorize edilmiştir. C0: Venöz hastalık ile ilgili gözlemlenebilir belirti yok. C1: Telanjiektaziler veya retiküler venlerin varlığı. C2: Bozulmuş ve palpe edilebilir subkutan varisli damarlar. C3: Cilt rengi değişiklikleri olmaksızın ödem. C4: Venöz durumlarla ilişkili cilt değişiklikleri. C5: İyileşmiş venöz ülserler. C6: Venöz yetersizlik nedeniyle aktif venöz ülser (4). Ultrason muayenesi, derin ve yüzeyel ven trombozunu dışlamak için supin pozisyonda gerçekleştirilmiştir. Bunun ardından hastalar, dik pozisyonda venöz yetersizlikleri açısından değerlendirilmiştir. Radyolog, Valsalva manevrasını kullanarak venöz valf fonksiyonunu değerlendirmiştir. "C" skoru ≥4 olanlar, daha ileri düzeyde venöz hastalık olarak kabul edilmektedir.

GSV, spontane solunum koşullarında ve uzuvlar nötr pozisyonda iken kaydedilmiştir. Her bir hasta segmentinde yedi saniye süreyle standartlaştırılan Valsalva manevrası, 0,5 saniyeden fazla süren retrospektif akış olarak tanımlanan önemli reflüyü tespit etmek için kullanılmıştır (1-3). Çap ve reflü varlığı, hastalar dik pozisyonda ölçülmüştür. Ölçümler, uyluğun proksimal ve distal üçte biri ve saphenopopliteal kesişimden 5 cm distal küçük saphenöz ven için GSV'i içeriyordu. GSV çapı (saphenofemoral kesişim ve diz seviyesinde) ile CEAP skoru, perforatör venlerin prevalansı ve KVY sıklığı gibi çeşitli parametreler arasındaki ilişkiyi değerlendirmek için karşılaştırmalı analizler yapılmıştır.

İstatistiksel Analiz

GSV çapı ile yukarıda belirtilen parametreler arasındaki ilişkiyi incelemek için istatistiksel analiz yapılmıştır. Tanımlayıcı istatistikler, korelasyon analizi, ROC analizi ve çıkarsama testleri veri değerlendirme amaçlı kullanılmıştır, analizlerde anlamlılık seviyeleri $p < 0,05$ olarak belirlenmiştir. Çalışma etik yönergelere ve ilkelere uygun olarak gerçekleştirilmiş olup, tüm katılımcılar çalışmaya katılmadan önce bilgilendirilmiş onam sağlamıştır. Veri gizliliği ve katılımcı mahremiyeti çalışmanın süresince sıkı bir şekilde korunmuştur. Yerel bir bilimsel araştırma komitesinden etik onay alınmıştır (karar numarası: 2022.09.293).

Sonuçlar

Katılımcıların ortalama yaşı 51,48 ± 25,68 yıl (± SD, min-max: 18-65) idi. Katılımcılar arasında 327 birincil venöz yetersizlik hastası ve 15 sekonder etiyolojili birey (posttrombotik, derin ven trombozu geçmişi) bulunmaktaydı. Çalışma sonrasında saphenofemoral kesişimde ölçülen büyük saphenöz venin ortalama çapı 6,18 ± 2,22 mm (± SD, min-max: 3-16) olarak belirlenmiştir. Benzer şekilde, diz seviyesinde ölçülen GSV'nin ortalama çapı 2.66 ± 2.10 mm (± SD, min-max: 1,3-14) olarak tespit edilmiştir.

Reflü varlığı çalışmada değerlendirilmiş olup, katılımcılardan 137'sinin reflüsü yok, 12'sinin sadece büyük saphenöz veninde reflü, 87'sinin hem büyük saphenöz ven hem de saphenofemoral kesişiminde reflü, 41'inin sadece saphenofemoral kesişiminde reflü, 7'sinin küçük saphenöz veninde reflü, 7'sinin hem küçük saphenöz ven hem de saphenofemoral kesişiminde reflü ve 5'inin küçük saphenöz ven, saphenofemoral kesişim ve büyük saphenöz veninde reflüsü olduğu tespit edilmiştir. Ayrıca, 103 hastada telanjiektaziler (C1) ve 292 hastada telanjiektazi yoktu. Varisli damarlar (C2) 100 hastada, bacak ödemi (C3) 27 hastada, ve 27 hastada ayak bileği renk değişikliği geçmişi (C4) tespit edilmiştir. Ayrıca, 22 hastada ülser ile ilişkili müdahaleler veya tedavi geçmişi bulunmaktadır (C5, C6). Çalışmada CEAP skorları değerlendirilmiş olup, 84 hastanın skoru 0, 74 hastanın skoru 1, 131 hastanın skoru 2, 58 hastanın skoru 3, 20 hastanın skoru 4, 18 hastanın skoru 5, ve 10 hastanın skoru 6 olarak belirlenmiştir. Çalışma, saphenofemoral kesişim ve diz seviyesinde büyük saphenöz venin çapındaki artışla birlikte reflü varlığında istatistiksel olarak anlamlı bir artış olduğunu göstermiştir ($p < 0,005$). GSV için saphenofemoral kesişiminde 7,85 mm kesme değeri seçildiğinde, KVY %31,0 duyarlılık ve %84,1 özgüllük ile tespit edilmiştir (AUC (CI): 0,555 (0,442-0,667), p-değeri: 0,343, Youden İndeksi: 0,152). GSV için saphenofemoral kesişiminde 7,05 mm kesme değeri seçildiğinde, KVY %34,0 duyarlılık ve %78,1 özgüllük ile tespit edilmiştir (AUC (CI): 0,555 (0,442-0,667), p-değeri: 0,343, Youden İndeksi: 0,124). GSV için diz seviyesinde 3,95 mm kesme değeri seçildiğinde, KVY %69,0 duyarlılık ve %75,8 özgüllük ile tespit edilmiştir (AUC (CI): 0,705 (0,601-0,809), p-değeri: 0,001, Youden İndeksi: 0,448). Ayrıca, cilt altında genişlemiş varisli damarlar bulunan vakalar ile bulunmayan vakalar arasındaki GSV çapı üzerinde anlamlı bir fark gözlenmiştir ($p < 0,005$), varisli damarları olan vakalarda ortalama GSV çapı 7,15 mm, olmayan vakalarda ise 6,39 mm olarak tespit edilmiştir. Regresyon analizinde, GSV çapı arttıkça CEAP skorunda anlamlı bir artış gözlemlenmiştir ($p <0,001$).

Saphenofemoral kesişimindeki büyük saphenöz ven çapı ile ayaktaki renk değişikliği geçmişi arasında zayıf pozitif korelasyon bulunmuştur (Pearson korelasyon katsayısı = 0,297). Saphenofemoral kesişimindeki büyük saphenöz ven çapı ile genişlemiş perforatör venlerin varlığı arasında ise orta düzeyde pozitif korelasyon gözlemlenmiştir (Pearson korelasyon katsayısı = 0,340). GSV için saphenofemoral kesişiminde 7,95 mm kesme değeri seçildiğinde, CEAP skoru

≥4 (gelişmiş venöz hastalığı gösteren) %92,9 duyarlılık ve %86,3 özgüllük ile tespit edilmiştir (AUC (CI): 0,911 (0,875-0,946), p-değeri: 0,001, Youden İndeksi: 0,792). GSV için diz seviyesinde 4,45 mm kesme değeri seçildiğinde, CEAP skoru ≥4 (gelişmiş venöz hastalığı gösteren) %85,7 duyarlılık ve %80,4 özgüllük ile tespit edilmiştir (AUC (CI): 0,916 (0,875-0,956), p-değeri: 0,001, Youden İndeksi: 0,661).

Tablo 1. Hastaların genel verileri

Çap (cm)	Toplam hasta sayısı	Toplam KVY hastası sayısı	Toplam KVY hastası yüzdesi
0-3	0	0	0
3-5	76	52	%68,42
5-7	120	85	%70,83
7-9	37	26	%70,27
9+	27	18	%66,67

Tablo 2. VSM çapları ve yetmezlik ilişkisi

VSM Çap Aralığı SFJ'de (mm)	GSV Reflü (%)	SFJ Reflü (%)	SSV Reflü (%)
0-5	10	5	1
5-10	20	15	5
10-15	35	30	20
15-20	50	45	30
VSM Çap Aralığı Dizde (mm)	GSV Reflü (%)	SFJ Reflü (%)	SSV Reflü (%)
0-5	5	3	1
5-10	15	10	5
10-15	25	20	10
15-20	40	35	25

Tartışma

CEAP sınıflaması KVY değerlendirilmesinde klinik olarak sıklıkla kullanılmasına rağmen, bu sınıflamadır. EAP kategorileri genellikle günlük kullanım için pratik olmadığından, genelde yalnızca "C" kategorisi sıkça kullanılmaktadır (4). Klinik bulguları sınıflandıran ve cerrahi müdahaleye karar vermek için nesnel bir puanlama sistemi sunan bir sınıflama olmasına rağmen, radyolojik uygulamalarda evrensel olarak kabul edilmiş bir puanlama sistemi hala yoktur. Geçmişte, akış hacmine göre reflüyü sınıflandıran bazı sınıflamalar kullanılmıştı, ancak bunlar artık geçerli değildir (5). Çalışmamızın sonuçları, çalışma popülasyonu içinde büyük saphenöz venin (GSV) çapında önemli bir varyasyon olduğunu göstermektedir. Büyük saphenöz venin boyutu, venöz yetersizlik (VY) semptomlarıyla yakından ilişkili olabilecek önemli bir klinik belirteç olabilir (6). Ayrıca, CEAP "C" puanındaki klinik bulgular ile saphenöz ven çapındaki artış arasında önemli bir ilişki keşfettik. Hacim aşırı yükü veya artmış hidrostatik basıncın neden olduğu damar genişlemesi, valf yaprakçıklarının etkin bir şekilde kapanmasını engellediğinden damar genişlemesine yol açar (6). Venöz çapın artması, valf yetmezliğine yol açabilir ve bu da daha fazla kaudal venöz genişlemeye ve artan valf yetmezliğine neden olabilir (6). Yüzeyel venöz sistem, basınçtaki değişikliklerden hızlı ve kolay bir şekilde etkilenir ve genellikle çapta bir artış ile birlikte KVY gözlemlenir (6). Durmaz ve arkadaşları (6), artan çap ile KVY arasında önemli bir ilişki gözlemlemişlerdir; venöz yetersizlik bulunan alt ekstremitelerdeki saphenöz ven çaplarının, venöz yetersizlik bulunmayanlarla karşılaştırıldığında istatistiksel olarak anlamlı derecede daha büyük olduğunu belirtmişlerdir (p<0.001). Ayrıca çapın, KVY için dolaylı bir gösterge olabileceğini bildirmişlerdir; saphenöz ven çapı tek başına önemli reflü için bağımsız bir gösterge olamaz, ancak ek bir parametre olarak faydalı olabilir.

Çalışmamız, çalışma popülasyonu içinde büyük saphenöz venin çapında önemli bir varyasyon göstermiştir. GSV çapındaki artış, reflü varlığı ile ilişkilendirilmiştir. GSV çapı, saphenofemoral kesişiminde 7,85 mm'den büyük veya diz seviyesinde 3,95 mm'den büyük olduğunda, reflü varlığı için yüksek özgüllük bulunmaktadır. Ayrıca, genişletilmiş varisli damarların varlığı ile önemli bir fark gözlenmiştir. Bu bulgular, GSV çapındaki değişikliklerin KVY'nin ilerlemesi üzerindeki potansiyel etkisini ön plana çıkarmaktadır.

Kim ve arkadaşları (7), GSV'nin hangi segmentinin venöz reflü nedeniyle en duyarlı ve genişlemeye en yatkın olduğunu araştıran bir çalışma gerçekleştirmiştir. Bu çalışmada, reflüsü olan uzuvlardaki GSV çapının, reflüsü olmayanlara göre LT segmentinde (4,7 mm vs. 4,2 mm; P <0,001) anlamlı derecede daha büyük olduğu bulunmuştur; en yüksek alan altında alma operatörü karakteristik eğrisi ise LT segmentinde 0,642 olarak bildirilmiştir. Bizim çalışmamızda, kesme değeri midthigh segmentinde 7 mm olarak bulunurken, Kim ve arkadaşları (7) diz seviyesinde ve baldırda tanı için en duyarlı olanın 5 mm eşik değeri olduğunu bildirmiştir (P = 0.025). Midthigh ve baldır segmentleri için reflü tespitinde en duyarlı kesim değerlerinin ayrı ayrı hesaplanmasının daha faydalı olacağına inanıyoruz. Orta Doğu ve Asya'daki yoğun klinik merkezlerde, klinik uygulamadaki prosedür süresi çok kısadır. Bu sınırlama genellikle radyologların baldır seviyesindeki GSV muayenesine daha az dikkat etmelerine yol açmaktadır. Dikkatin daha yoğunlaştığı midthigh segmentinde kesme değerinin bulunması, alt ekstremitenin diğer bölgelerini de dikkatlice değerlendirmek için bir uyarı görevi görecektir (8,9,10). Genellikle, GSV'nin çapı venöz reflü varlığında genişler

ve bu genişlemenin derecesi GSV içindeki reflünün büyüklüğü ve yeri temelinde değişebilir (7). Son zamanlarda, bazı sigorta şirketleri, eksenel venöz yetersizlik tedavisi için kapsam kararı verirken belirli GSV çapı eşiklerini kullanmaktadır (11).

Son zamanlarda, birçok çalışma GSV çapları ile daha yüksek CEAP skorları arasında bir ilişki göstermiştir (11). Farklı bir perspektiften, CEAP skoruna odaklanmak yerine, Gibson ve arkadaşları (11) KVY'li hastalarda GSV çapları ile hasta yaşam kalitesi arasındaki ilişkiyi inceleyen bir çalışma gerçekleştirmiştir. Bu çalışmada, GSV'de en az 5 mm olan semptomatik KVY hastalarında yaşam kalitesini değerlendiren çok sayıda anket yapılmıştır. GSV çapının, varisli damarların bir hastanın yaşam kalitesi üzerindeki etkisini değerlendirmek için yetersiz bir gösterge olduğunu bildirmişlerdir. Sadece GSV çapını dikkate almanın KVY için tıbbi tedavi sağlarken yetersiz olduğunu ve tedavi kararları için ek parametrelerin gerektiğini bulmuşlardır. Bizim çalışmamızda, genel olarak 7,95 mm'den fazla GSV çapına sahip hastalarda daha ileri venöz hastalık (C4-6) gözlemlenmiştir. Ancak, GSV çapı 5 mm veya daha az olan bazı hastalarda reflü de tespit edilmiştir; özellikle tüm gün ayakta duran, bağ dokusu bozuklukları olan veya herhangi bir etyolojik faktör geçmişi bildirmeyen hastalarda. Buradan, geniş bir GSV çapının reflü varlığının önemli bir göstergesi olduğunu, ancak çok hafif GSV kalibrasyonlarının etyolojik faktörleri olan hastalarda yüksek akış reflüsüne sahip olabileceğini sonucuna varıyoruz. Bu hastalarda tıbbi tedavi başlatmak için, akış ölçümü veya hastanın geçmişinde etyolojik faktörlerin dikkatlice incelenmesinin gerekli olduğuna inanıyoruz.

Bu çalışmanın birkaç önemli sınırlaması bulunmaktadır; öncelikle hastalar sınırlı bir süre boyunca takip edilmiştir. Yaşam tarzı seçimleri ve vücut kütle indeksi sonuçları etkileyebilir. Bu faktörler, venöz sağlığı önemli ölçüde etkileyebilir, ancak çalışma tasarımında sistematik olarak dikkate alınmamıştır. Ayrıca, uzun dönemli takip eksikliği, büyük saphenöz venin çapındaki değişikliklerin uzun vadeli sonuçlarını ve bunların kronik venöz yetersizlik ile ilişkisini değerlendirme yeteneğini sınırlamaktadır. Ayrıca, GSV çapı için belirlenen kesim değerleri, farklı popülasyonlarda evrensel olarak uygulanabilir olmayabilir. Anatomideki değişkenlik, tüm hasta gruplarında reflüyü doğru bir şekilde tahmin edemeyebilir ve bulguların genelleştirilebilirliğini sınırlamaktadır.

Sonuç olarak, bu çalışma GSV çapı ile KVY belirtilerinin varlığı arasında önemli bir ilişki ortaya koymuştur. Bulgular, artan GSV çapının yalnızca daha yüksek bir CEAP skoru ile ilişkili olmadığını, aynı zamanda venöz reflü olasılığı ile de korele olduğunu göstermektedir. Ayrıca, sonuçlar GSV çapının KVY'nin klinik değerlendirilmesi ve yönetiminde önemli bir parametre olarak değerlendirilmesinin önemini vurgulamaktadır. Venöz reflü hastalığın ilerlemesinde önemli bir rol oynadığından, GSV çapı için eşik değerlerin anlaşılması, bilinçli tedavi kararları alınmasına yardımcı olabilir. Bu bilgilerin, KVY'nin yönetimi için daha iyi tanı ve tedavi stratejileri aracılığıyla hasta sonuçlarını önemli ölçüde iyileştirebileceğine inanıyoruz.

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Research Article

The effect of the Japanese Investigation Committee classification on hip joint survival after core decompression therapy in pre-collapsed avascular necrosis of the femoral head

Japon İnceleme Komitesi sınıflandırmasının, femur başı prekollaps avasküler nekrozunda kor dekompresyon tedavisi sonrası kalça eklemi sağkalımı üzerindeki etkisi

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Abstract

Aim: This study aimed to determine the failure rate of pre-collapse avascular necrosis (AVN) of the femoral head treated with core decompression (CD) and risk factors affecting the progression of the disease in patients by using an easily applicable staging system.

Material and Methods: A total of 174 hips from 134 patients diagnosed with precollapse AVN and treated with CD were retrospectively examined. Each hip was classified using the Japanese Investigation Committee (JIC) classification. The endpoint for joint survival following treatment was defined as the occurrence of total hip arthroplasty (THA). The risk analysis on joint survival of various independent variables (treatment type, age, gender, etiology) and the frequency of THA 2 and 5 years after treatment was calculated.

Results: The mean age of the patients was 44.0 ± 15.0 years, with the majority being male (71.8%). THA was performed in 28.7% of treated hips within two years and 40.2% within five years. The frequency of THA application within two years was 2% for type A, 8% for type B, 40% for type C1 and 50% for type C2. Age ($p=0.033$), type C1 ($p=0.028$) and type C2 ($p<0.01$). The rate of post-treatment THA in patients with AVN due to steroid use was found to be significantly higher than in other etiologies ($p<0.001$). The average survival time of type C1 hips despite treatment is 58.5 months, while the average survival time of type C2 hips is 42.8 months.

Conclusion: In patients with type C1 and C2, hip survival times are significantly shorter than those of type A and type B hips, regardless of previous treatment, and it is a risk factor for THA. Additionally, history of steroid use and age were found to be independent risk factors that shorten hip joint survival.

Keywords: avascular necrosis, core decompression, femoral head, classification, total hip arthroplasty

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Öz

Amaç: Bu çalışma, kor dekompresyon ile tedavi edilen prekollaps femur başı avasküler nekrozunun başarısızlık oranını ve hastalarda hastalığın ilerlemesini etkileyen risk faktörlerini kolay uygulanabilir bir evreleme sistemi kullanarak belirlemeyi amaçlamadı.

Gereç ve Yöntemler: Prekollaps avasküler nekroz tanısı almış ve kor dekompresyon ile tedavi edilmiş 134 hastanın 174 kalçası retrospektif olarak incelendi. Her kalça, Japon İnceleme Komitesi (JIC) sınıflandırması kullanılarak sınıflandırıldı. Tedavi sonrası eklem sağkalımının sonlanma noktası, total kalça artroplastisi yapılması olarak tanımlandı. Farklı bağımsız değişkenlerin (tedavi türü, yaş, cinsiyet, etiyoloji) eklem sağkalımına etkisi ve tedaviden sonraki 2 ve 5 yıl içinde THA sıklığı hesaplandı.

Bulgular: Hastaların ortalama yaşı 44.0 ± 15.0 yıl olup, çoğunluğu erkekti (%71,8). Tedavi edilen kalçaların %28,7'sine iki yıl içinde ve %40,2'sine beş yıl içinde THA yapıldı. İki yıl içinde THA uygulanma sıklığı tip A için %2, tip B için %8, tip C1 için %40 ve tip C2 için %50 idi. Yaş (p=0,033), tip C1 (p=0,028) ve tip C2 (p<0,01) anlamlı bulundu. Steroid kullanımına bağlı AVN'li hastalarda tedavi sonrası THA oranı diğer etiyolojilere göre anlamlı olarak daha yüksek bulundu (p<0,001). Tip C1 kalçaların tedaviye rağmen ortalama sağkalım süresi 58,5 ay iken, tip C2 kalçaların ortalama sağkalım süresi 42,8 aydı.

Sonuçlar: Tip C1 ve C2 olan hastalarda, kalça sağkalım süreleri, önceki tedaviden bağımsız olarak tip A ve tip B kalçalara göre anlamlı derecede daha kısadır ve bu, THA için bir risk faktörüdür. Ayrıca, steroid kullanım öyküsü ve yaş, kalça eklemi sağkalımını kısaltan bağımsız risk faktörleri olarak bulunmuştur.

Anahtar Kelimeler: avasküler nekroz, kor dekompresyon, femur başı, sınıflandırma, total kalça artroplastisi

Introduction

Femoral head avascular necrosis (AVN) is a multifactorial disease affecting young and middle-aged adults [1]. The most common risk factors are long-term intake of alcohol and corticosteroids [2, 3]. Although the mechanism of the development of the disease is not fully known, osteonecrosis in the subchondral bone and subsequent collapse of the joint surface cartilage occurs [4]. Spontaneous recovery is very rare in individuals with untreated AVN, so subchondral collapses that develop may cause early osteoarthritis, leading to the necessity for total hip arthroplasty (THA), including in young patients. Studies show that osteoarthritis due to AVN is responsible for 5 to 12% of all THA [5, 6]. For this reason, the most important prognostic indicator in patients with AVN is the collapse of the femoral head cartilage, and THA becomes inevitable in the subsequent period [7, 8].

Treatment of AVN is based on the stage of the disease. In the early stages of the disease, various joint-preserving procedures are applied to protect the joint and prevent collapse of the femoral head. Especially in young adults, early diagnosis and regenerative treatments are critical for hip joint survival. For this purpose, several interventions can be performed to postpone and reduce the possibility of hip replacement, including physical therapy, pharmacotherapy, bone flap transplantation with vascular pedicles, and core decompression (CD) of the femoral head [9-11]. CD is the most commonly used treatment for early AVN, and in recent years, bone marrow-derived mesenchymal stem cell concentrates (BMAC) have been added to this [3, 9, 12]. The ability of magnetic resonance imaging (MRI) to diagnose the disease with more than 90% sensitivity in the early stages has enabled us to apply more joint-preserving procedures in recent years [13, 14]. However, despite hip-preserving procedures applied in patients with early-stage AVN, femoral head collapse develops at rates ranging from 14 to 60.5%, depending on the volume, location, and depth of necrosis [15-17]. It has been reported that early collapse occurs in nearly one-third of pre-collapse cases with AVN, regardless of joint-preserving treatment methods, and many of these patients eventually require THA due to the development of secondary osteoarthritis [18].

This study aimed to determine the failure rate of pre-collapse AVN of the femoral head treated with CD and risk factors affecting the progression of the disease in patients by using an easily applicable staging system.

Material and Methods

This study was conducted in accordance with the ethical criteria of the 1964 Declaration of Helsinki and was approved by the institutional human research ethics committee (No: 2023-777). Between March 2013 and June 2018, 174 hips of 134 patients (92 men, 42 women) who were diagnosed with pre-collapsed AVN and treated with augmentation (BMAC) and non-augmentation CD (CD-BMAC and CD) methods were performed. The data were examined retrospectively. During treatment, bilateral hip involvement was present in 40 patients (29.8%). The median age

of the patients was 44 years (19-75 years), and the average follow-up period after treatment was 81 months (62-115 months).

The diagnosis of the patients was made based on history, physical examination, and radiological imaging, and the diagnosis of pre-collapse AVN was confirmed using two-way hip radiography, computed tomography (CT) of the affected hip, and MRI. Accordingly, diagnosed patients were grouped according to the JIC classification, a staging system based on the involvement of the weight-bearing surface of the femoral head [19]. There were 21 affected hip joints in the Type A group, 32 in the Type B group, 68 in the Type C1 group, and 53 in the Type C2. Forty-five patients had a history of corticosteroid use, and 14 patients had a history of excessive alcohol use. Additionally, six patients had a history of Systemic Lupus erythematosus, four patients had a history of hematological malignancy, and two patients had a history of sickle cell anemia. No etiological cause was detected in 63 patients, and they were classified in the idiopathic AVN group. While 78 of the diagnosed patients underwent only CD, 96 underwent CD-BMAC. The exclusion criteria included patients diagnosed with AVN and subchondral collapse, patients diagnosed with traumatic AVN, patients with AVN who underwent hip-preserving treatment options other than CD or CD-BMAC (osteotomy, bone graft, vascularized fibula, etc.), and patients under the age of 18.

In treated patients, the final hip survival time was defined as the time of THA. Accordingly, patients who underwent THA within two years after treatment were collected in Group 1, while patients who did not undergo THA were collected in Group 2. Patients in both groups were examined regarding JIC classification, etiology, treatment method, age, and gender, and risk analysis was performed. In addition, the hip survival of the patients in the second and fifth years was examined, and the average hip survival time was estimated depending on the variables.

Surgical technique

All patients underwent CD under general anesthesia. Under fluoroscopic guidance, three 2.5 mm endobutton guide wires were advanced into the affected hips from the greater trochanter along the long axis of the femoral neck to reach the subchondral necrotic area. After determining the most centrally placed guide wire, the decompression process was completed with a 4.5 mm endobutton thread. In patients who underwent augmentation with BMAC, 100 ml of bone marrow was taken percutaneously from the iliac crest for a single application, and intraoperative processing and concentration were performed. Approximately 4-5 ml of bone marrow concentrate was injected into the necrotic area with a special tip through the endobutton.

Statistical analysis

All data were analyzed with IBM SPSS Statistics for Windows 22.0 (IBM Corp., Armonk, NY, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean (standard deviation [SD]) values while non-normally distributed variables are given as median (25th-75th quartile) values. Categorical variables are given as numbers and percentages, and inter-group comparisons were conducted with Chi-square and Fisher exact tests. Binary Logistic regression analysis was performed to find variables associated with increased risk of THA during the two-year follow-up period. Kaplan-Meier analysis was used to determine the duration of THA in the second and fifth years of the patients. Significance was accepted at $P < 0.05$ (*) for all statistical analyses.

Results

The mean age of the patients was 44.0 ± 15.0 years, with the majority being male (71.8%). Demographic and clinical data of the patients included in the study are given in Table 1.

Of the 174 hips diagnosed with pre-collapsed AVN, CD was applied as a treatment method to 78 (44.8%), and CD-BMAC combination was applied to 96 (55.2%). The rate of progression to THA in treated hips within two years was 28.7% (50 hips), while the rate of progression within five years was calculated as 40.2% (70 hips). When the group that underwent THA (Group 1) and the group that did not (Group 2) were compared within two years, the male/female ratio was found to be similar in both groups (p=0,952). The proportion of patients with bilateral hip involvement was statistically similar in both groups (p=0,17). According to the JIC classification, the frequency of type A and type B hips was higher in the 2nd group, while the frequency of type C2 hips was significantly higher in the 1st group (p<0,001). When examined etiologically, the frequency of steroid intake was higher in group 1, while the frequency of idiopathic AVN was significantly lower (p<0.001). Alcohol intake history was similar between both groups (p>0,05). It was determined that the treatment applied in patients with AVN (CD or CD-BMAC) was statistically ineffective on hip survival (p = 0,618).

Age, stage C1 and C2 were found to be associated with the increased risk of THA in 2 years (p<0.05), while gender, bilateral involvement (and previous surgery method (0.715) were not associated with the risk of THA in 2 years. (p>0.05). Table 2 shows the results of the logistic regression analysis. The risk of THA in two years was higher in glucocorticoid and alcohol-induced AVN than in idiopathic AVN but was similar in other pairwise comparisons of etiological causes (p=0.02). Data are given in Table 2.

Table 1. Demographic and clinical features of the patients

	All patients (n=134, 174 hips)	Non-THA in 2 years (n=92, 124 hips)	THA in 2 years (n=42, 50 hips)
Age (median; IQR or mean ± SD)	44.0 (15.0)	44.0 (16.0)	47.0 (15.0)
Gender (n/%)			
Female	49 (28.2)	36 (29.0)	14 (28.0)
Male	125 (71.8)	88 (71.0)	36 (72.0)
Bilateral involvement (n/%)	40 (29.8)	32 (25.8)	8 (19.0)
JIC (n/%)			
A	21 (12.1)	20 (16.1)	1 (2.0)
B	32 (18.4)	28 (22.6)	4 (8.0)
C1	68 (39.1)	48 (38.7)	20 (40.0)
C2	53 (30.5)	28 (22.6)	25 (50.0)
Etiology (n/%)			
GC	59 (33.9)	24 (19.4)	24 (48.0)
Alcohol	19 (10.9)	8 (6.4)	8 (16.0)
İdiopathic	77 (44.3)	52 (41.8)	12 (24.0)
Hematological malignancy	5 (2.9)	3 (2.4)	1 (2.0)
SCA	2 (1.1)	1 (0.8)	1 (2.0)
SLE	12 (6.9)	4 (3.2)	4 (8.0)
Surgery method			
CD-B	96 (55.2)	67 (54.0)	29 (58.0)
CD	78 (44.8)	57 (46.0)	21 (42.0)
Time to THA (months)	-	16.0 (9.3)	-
Follow-up time (months)	72.0 (57.3)		

*THA: Total hip arthroplasty, IQR: Interquartile range, GC: Glucocorticoid, SCA: Sickle cell anemia, SLE: Systemic lupus erythematosus, CD-B: Core decompression bone graft, CD: Core decompression

Table 2. Binary logistic regression analysis of variables associated with increased risk of total hip arthroplasty in 2 years

Variables	OR	95% CI lower-upper	P-value
Age	1.036	1.002-1.070	0.036
Gender	0.857	0.384-1.915	0.707
JIC stage B	2.653	0.268-26.295	0.405
JIC stage C1	8.312	1.013-68.190	0.039
JIC stage C2	16.349	1.987-134.534	0.009
Bilateral involvement	0.632	0.251-1.588	0.328
Previous surgery method	1.070	0.512-2.233	0.858

CI, confidence intervals; JIC, Japanese Investigation Committee; OR, odds ratio

According to binary logistic regression analysis, age (p=0,033, OR:1.045), type C1 hip (p=0,029, OR:11,035), type C2 hip (p<0,01, OR:23.699), and history of steroid intake (p=0,019, OR: 14.876) were identified as risk factors associated with the probability of progression to THA within two years after treatment. Gender (p=0,663), bilateral hip joint involvement (p=0,196), and type of previous surgical method (p=0,715) were not found among the risk factors. When examined etiologically, it was found that the probability of THA application within two years was the lowest in patients with idiopathic AVN (p =0,046, OR: 0,220).

According to Kaplan-Meier analysis, the average time to THA of our treated patients with pre-collapse AVN was estimated as 59,310 months (SD: 2,366; 95% CI: 54,672-63,949 months), and in Type A hips, the average time to THA was 80,952 months (SD: 2,974; 95% CI: 75.123-86.782 months), while in type C2 hips this period was calculated as 42,868 months (SD: 4.141; 95% CI: 34.752-50.984 months) on average (Figure 1). When examined etiologically, the average time to THA after treatment in patients with a history of steroid intake is 49,746 months (SD: 4,240; 95% CI: 41,436-58,036 months), while this period is 67,532 months (SD: 3,028; 95% CI) in patients with idiopathic AVN. (61,598-73,467 months) (Figure 2).

Discussion

This study examined the effects of CD and the CD-BMAC combination on joint preservation in femoral head AVN treatment. THA was performed in 28.7% of patients within two years and 40.2% within five years. Age, type C1 and C2 hips in the JIC classification, and steroid use were identified as factors increasing the risk of THA. The treatment method (CD or CD-BMAC) was not statistically significant in influencing hip joint survival.

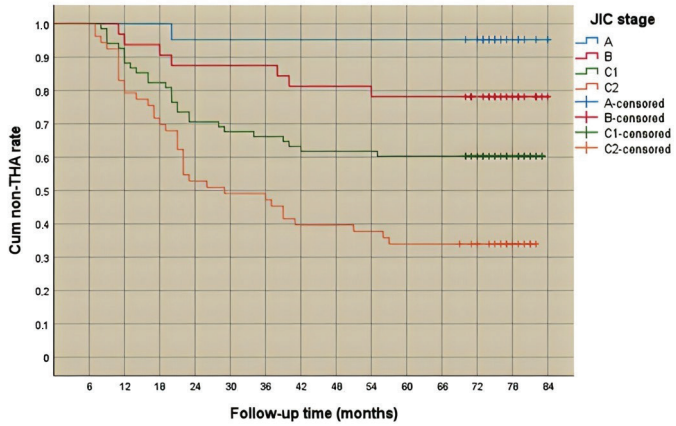

Figure 1. A: Kaplan-Meier graphic of time of not undergoing total hip arthroplasty according to Japanese Investigation Committee stage.

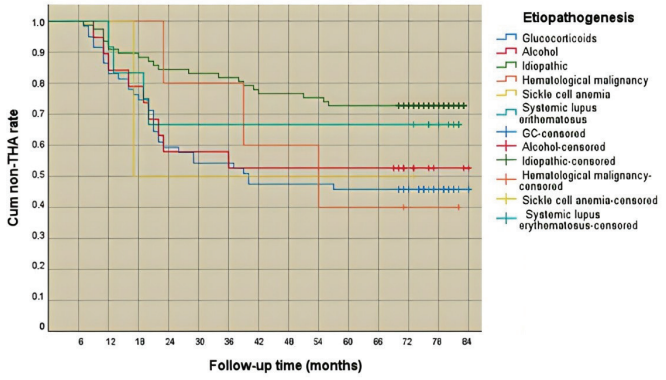

Figure 2. Kaplan-Meier graphic of time of not undergoing total hip arthroplasty according to etiopathogenesis.

Various classification systems have been widely used in making treatment decisions, choosing treatment methods, and estimating average hip survival in AVN. The effectiveness of each classification system in determining treatment and prognosis still needs clarification. However, the common view is that an ideal classification method should meet the following conditions. 1. It should be simple and easy to apply; 2. It should be reproducible and reliable among observers, 3. It should be able to predict the progression of AVN successfully; 4. It should be able to contribute to the choice of treatment. In our study, it has been shown that the JIC classification largely meets the above conditions and is successful in predicting hip survival and disease progression considering the JIC types. While the two-year hip joint survival rates of 21 JIC type A hips and 32 type B hips treated from our patients were 95.2% and 87.5%, respectively, in the five years, this rate was found to be 95.2% and 81.3%, respectively. However, two- and five-year survival rates decrease dramatically in type C1 and especially type C2 hips despite treatment. In our study, the two- and five-year survival rates of 68 type C1 hips were found to be 70.5% and 60.2%, respectively, while this rate was calculated to be 52.8% and 32%, respectively, for 53 type C2 hips. As a result, while hip joint survival continued greatly with treatment in JIC type A and type B hips, hip joint survival was at a different level despite treatment in type C1 and especially type C2 hips.

The widespread use of MRI in diagnosing and treating AVN has been a historical turning point. With the increased use of MRI, the rate of patients diagnosed in the pre-collapse stages and undergoing joint-preserving surgery has increased. For this reason, the importance of classification systems has increased, and researchers have focused on this issue again. Mont et al. conducted a literature review to define the methods used for AVN classification. They found that Ficat and Arlet, Association Research Circulation Osseous (ARCO), Steinberg, and modified Kerboul classifications were used in most studies [20-24]. The Ficat-Arlet and Steinberg staging systems, commonly utilized today, are insufficient in assessing progression, particularly in pre-collapse avascular necrosis (AVN), as they do not consider critical variables such as the size and location of necrosis, which play significant roles in the disease's progression [25, 26].

Additionally, users do not prefer the Steinberg staging system due to its complexity. The ARCO classification system was developed to create an international classification system [27]. However, since its most important shortcoming was that it did not include the location of necrosis, the explanations of the Japanese Investigation Committee were added in later revisions. With the latest updates, it has become a complex classification system containing six stages and different subgroups within these stages [28]. The reliability and reproducibility of the ARCO classification in its final form within and between users continues to be a matter of debate. In the Kerboul method, the necrosis volume was determined with some formulations by measuring the angle of the femoral surface where necrosis occurred using midcoronal and midsagittal magnetic resonance images [22-24]. However, since conversion tables and calculators are required to calculate the affected femoral head volume, it has yet to find widespread use among observers [29, 30].

The most important feature that distinguishes the JIC classification from other methods is that it evaluates the location and size of necrosis with a sensitive imaging method such as MRI [19]. In this system, it has been argued that as the lesions grow, they progress from medial to lateral and face more

acetabular load, resulting in early collapse and degenerative arthritis [31, 32]. In a study that investigated the connection between necrosis volume and disease progression using the 3D MRI method, Nishii et al. emphasized the importance of necrosis volume. However, they emphasized that even if the lesions are volumetrically small, collapse occurs much faster in laterally located lesions [33]. Sultan et al., in their study comparing the most preferred classification systems, emphasized that the JIC classification is more promising in following the disease prognosis and is simpler to use than others [32]. The results of Kuroda et al. supported this study. Their study found that the two-year collapse rate was 0% in type A and type B hips, while this rate was 36% in type C2 hips [34]. In our study, the disease had similar rates of hip joint survival.

One of the most important advantages of the JIC classification is its simple use. In this way, inter- and intra-observer reliability is high and can be easily repeated in different centers. In the study conducted by Nakamura et al., the interobserver reliability of the JIC classification was reported as 85% and the interobserver reliability as 82% [35]. In the study conducted by Takashima et al. in 2018, they compared Steinberg, Modified Kerboul, and JIC classifications in the same patient group [29]. Their study concluded that the reliability and reproducibility of the JIC classification were notably high, approaching perfection, making it more effective than the Steinberg and Kerboul classifications, particularly in predicting early-stage AVN progression. In our study, orthopedic surgeons who are experts in hip joints classified the affected hips without using any software or measurement programs.

Some remarkable findings were revealed in this study. Hip survival rates were worse in elderly patients and in patients with pre-collapse AVN due to steroid use, regardless of the treatment method. Our results were compatible with previous studies [36-39]. Another striking finding in our study is that the treatment (CD or CD-BMAC) did not affect hip joint survival. Many studies have investigated this issue before, but a definitive conclusion has yet to be reached. Although some studies claim that CD combined with BMAC treatment is more effective than CD treatment, others have not demonstrated one superiority over another [11, 17, 40, 41-43]. However, the common opinion is that CD and CD-BMAC treatments are clinically and radiologically effective in most early-stage AVN [29, 34, 40].

Our study has some limitations. First, the included patients had different etiological causes (steroids, alcohol, etc.). Depending on the etiology, the natural course of the disease may differ. Second, there is no intra-observer and inter-observer reliability study for the JIC classification. Third and the last, the time of THA application is taken as the final survival of the hip joint. Although our follow-up period seemed sufficient, patients may have been reluctant to have arthroplasty.

Conclusion

The JIC classification in pre-collapsed AVN is an effective method in choosing treatment and predicting the natural course of the disease. In type A and type B hips, CD or CD-BMAC gives good clinical and radiologic results and prolongs hip joint survival. However, especially in type C2 hips, the prognosis is poor, and hip survival times are short, regardless of treatment. Our study will make important contributions to other researchers developing treatment algorithms in the future. It will also guide patients and surgeons in predicting the natural course of the disease.

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Conflicts of Interest

The authors declare they have no conflicts of interest.

Ethics Approval

The study was approved by the Ankara Etlik City Hospital Clinical Research Ethics Committee (24/01/2024 - No: 2023-777).

Informed Consent

The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

Availability of Data and Material

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

Authors' contribution

Concept – E.A., Design- E.A., Data collection and/or processing - E.A., I.K., A.T., H.E.T., and A.F., Analysis and/or interpretation - E.A., I.K., A.T., H.E.T., and A.F., Writing – E.A., Critical review- I.K., A.T., H.E.T., and A.F. All authors read and approved the final version of the manuscript.

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Research Article

Does the incidence of post-COVID pulmonary complications in vaccinated individuals correlate with the types of vaccines they received?

BioNTech veya Sinovac ile aşılanmış bireylerde COVİD-19 sonrası akciğer komplikasyonlarının karşılaştırılması

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Abstract

Aim: Although several research have been undertaken to investigate the impact of the vaccination on long Coronavirus Disease 2019 (COVID-19) syndrome or post-acute sequelae, there is a lack of published evidence on the long-term effects of vaccines on lung-sequelae-related disease. Considering the limited global COVID-19 vaccine distribution, it is essential to establish the impact of vaccination in reducing pulmonary complications. Turkey has been offering COVID-19 vaccines from two platforms, including BNT162b2 (Pfizer-BioNTech, mRNA vaccine) and CoronaVac (Sinovac, inactivated vaccine). This study aimed to evaluate the efficacy of BioNTech and Sinovac vaccines in reducing post-COVID-19 pulmonary complications in individuals.

Material and Methods: A total of 94 patients COVID-19 pneumonia patients who were categorized based on the quantity of BioNTech or Sinovac vaccines they received before their first COVID-19 infection were included. The inclusion criteria consisted of a confirmed diagnosis of COVID-19 pneumonia through polymerase chain reaction testing, availability of the mentioned before and follow-up computed tomography scans, and administration of at least one dose of vaccine.

Results: The number of complications in patients fully vaccinated with Sinovac and who experienced post-COVID lung complications was significantly greater than in those vaccinated with BioNTech. The C-reactive protein and D-Dimer measurements of individuals who experienced complications in the Sinovac vaccinated group were significantly elevated on the index date.

Conclusion: The quantity of lung sequelae after COVID and laboratory parameters indicating this result were found to be higher in inactivated virus vaccines than in mRNA vaccines. This suggests that the protection of inactivated vaccines may be insufficient in severe cases.

Keywords: lung sequelae, vaccination, coronavirus disease, chest CT, inactivated vaccines, mRNA vaccines

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Öz

Amaç: Uzun Koronavirüs Hastalığı 2019 (KOVİD-19) sendromu veya akut sonrası sekeller üzerinde aşının etkisini araştırmak için çeşitli araştırmalar yapılmış olsa da, aşıların akciğer sekeli ile ilişkili hastalıklar üzerindeki uzun vadeli etkilerine dair yayımlanmış kanıtlar sınırlıdır. Küresel KOVİD-19 aşı dağıtımının sınırlı olması göz önüne alındığında, aşının akciğer komplikasyonlarını azaltmadaki etkisini belirlemek hayati önem taşımaktadır. Türkiye'de, KOVİD-19 aşıları BNT162b2 (Pfizer-BioNTech, mRNA aşısı) ve CoronaVac (Sinovac, inaktif aşı) dahil olmak üzere iki platformdan sunulmaktadır. Bu çalışma, BioNTech ve Sinovac aşılarının KOVİD-19 sonrası akciğer komplikasyonlarını azaltmadaki etkinliğini değerlendirmeyi amaçladı.

Gereç ve Yöntemler: İlk KOVİD-19 enfeksiyonlarından önce aldıkları BioNTech veya Sinovac aşılarının miktarına göre kategorize edilen toplam 94 KOVİD-19 pnömonisi hastası çalışmaya dahil edildi. Dahil etme kriterleri, polimeraz zincir reaksiyonu (PCR) testi ile doğrulanmış KOVİD-19 pnömonisi tanısı, belirli takip ve başlangıç bilgisayarlı tomografi taramalarının mevcut olması ve en az bir doz aşı uygulanmış olmasını içeriyordu.

Bulgular: KOVİD-19 sonrası akciğer komplikasyonları yaşayan ve Sinovac ile tam aşılanan hastalardaki komplikasyon sayısı, BioNTech ile aşılananlara göre anlamlı derecede daha yüksekti. Komplikasyon yaşayan Sinovac grubundaki bireylerin C-reaktif protein ve D-Dimer ölçümleri başlangıç tarihinde önemli ölçüde yüksekti.

Sonuç: İnaktif virüs aşılarında KOVİD sonrası akciğer sekel miktarı ve bu sonucu gösteren laboratuvar parametreleri mRNA aşısına göre yüksek bulunmuştur. Bu durum ağır vakalarda inaktive aşıların korumasının yetersiz olabileceğini düşündürmektedir.

Anahtar Kelimeler: akciğer sekeli, aşılama, koronavirüs hastalığı, göğüs BT, inaktive aşılar, mRNA aşıları

Introduction

Extensive research has been conducted since the emergence of the COVID-19 pandemic in late 2019, caused by the SARS-CoV-2 virus, to determine the clinical sequelae of COVID-19 infection. Because this pandemic has harmed millions of people [1–4].

Research indicates that individuals with COVID-19 may face an increased likelihood of experiencing acute and post-acute sequelae that affect different organ systems. Additionally, there is a higher risk of mortality associated with COVID-19 infection. While the efficacy of COVID-19 vaccines in preventing severe COVID-19 disease and death has been extensively studied, it is currently unknown whether vaccination reduces the risk of pulmonary-extrapulmonary complications and mortality. This is the main area of focus in ongoing research [2, 5]. The clinical symptoms that occur within 30 days of initial infection are called acute sequelae of COVID-19. On the other hand, complications that arise or continue beyond the acute phase are referred to as post-acute sequelae of SARS-CoV-2 (PASC), which is also known as post-COVID syndrome or long COVID [6, 7]. Although most patients typically recover from COVID-19 infection within two to four weeks of experiencing symptoms, studies has shown that there is an elevated risk of cardiovascular, pulmonary, and neurological complications, as well as overall mortality, that can persist for up to two years [8, 9]. COVID-19 pneumonia can range in severity from asymptomatic to critical respiratory failure necessitating mechanical ventilator support. Patients with severe COVID-19 infection and those who are seriously ill have a heightened risk of developing long-term complications [10].

Following the 2003 SARS-CoV-2 outbreak, 67% of patients experienced long-lasting lung fibrosis within a month following being infected, and certain abnormalities remained evident even after a span of seven years [11]. Prior studies on the long-term effects of COVID-19 on the lungs have revealed that over 50% of recovered individuals exhibited abnormalities in their thoracic computed tomography (CT) for several weeks following being infected. Ground glass opacities (GGOs) and pleuroparenchymal bands were all commonly observed [10, 12].

As per Ministry of Health data, Turkey has been offering COVID-19 vaccines from two prominent vaccine platforms, including BNT162b2 from BioNTech/Fosun Pharma (Pfizer-BioNTech, mRNA vaccine) and CoronaVac from Sinovac Biotech Limited (inactivated vaccine), to people who are 18 years and above. CoronaVac has been available since 13 January 2021, while BNT162b2 has been available since 12 April 2021. COVID-19 booster shots became accessible starting on June 30, 2021. Individuals were able to choose between BNT162b2 or CoronaVac for the first and second dose. The study conducted by

Sonmezer et al. demonstrated that administering third booster injections with BNT162b2 or CoronaVac offers substantial defence against severe COVID-19 infection and completely eradicates the chances of being hospitalised, admittance to a critical care unit, or mortality [13, 14].

Long COVID is invariably accompanied with a significant economic burden. Within this entity, the spectrum of symptoms and is quite broad. In addition to long COVID terminology, various terminologies such as post-acute COVID-19 syndrome, chronic COVID syndrome and long-haul COVID are used in the literature [15]. While numerous studies have been carried out to examine the impact of the vaccine on long-COVID syndrome or post-acute sequelae, the available researched information for the long-term consequences of vaccination on lung-sequelae-related disease is currently limited. Gao et al. conducted a comprehensive analysis of 18 independent studies on a population that received predominantly mRNA vaccines. The review revealed that administering a double dose of the vaccine seemed to provide protection from long-term COVID [16]. There have been no studies to date that have explored this problem by evaluating thorax CT images.

Given the world's inadequate COVID-19 vaccine coverage, it is critical to determine whether vaccination reduces pulmonary sequelae. The current research aims to evaluate the efficacy of BNT162b2 and CoronaVac, two COVID-19 vaccines authorised in Turkey, in preventing post-COVID pulmonary complications in individuals aged 18 and above. Our goal is to fill the knowledge deficit regarding this topic, in order to ascertain whether to proceed with vaccination using a specific type of vaccine.

Materials and Methods

This study obtained ethical approval from the Clinical Research Ethics Committee at Erzincan Binali Yildirim University (Protocol number: EBYU-KAEK-2023-11-002-EC-023567.003 / Date: 02 November 2023). Each patient gave written informed consent for the publication of this article using their data.

Study design and population

The study was carried out at a tertiary university hospital. We aimed to comprise our study population of newly diagnosed patients with COVID-19 pneumonia, younger than 65 years of age, who had not previously had COVID-19, were vaccinated with a single type of vaccine, and did not have any high-risk comorbid diseases. We looked at 685 lung CTs from the hospital's PACS that were diagnosed with COVID-19 pneumonia between April 1, 2021 and February 1, 2022. Firstly, 143 of these 685 patients who have never been vaccinated against COVID-19 were excluded from the study. Because in most of these patients, widespread sequelae findings were observed in the lung parenchyma. Some patients had received one dose of booster BNT162b2 after being vaccinated with two doses of Coronavac. We excluded 68 patients who had previously received this type of hybrid vaccination in order to conduct an objective evaluation of the vaccines' specific effectiveness on pulmonary sequelae. Of the remaining 474 patients, 36 patients were excluded from the study because they had COVID-19 reinfection and 332 were excluded from the study because did not have a CT images within the specified time intervals. Ultimately, after assessing laboratory values and previous CT images, 12 patients were excluded from the study due to the presence of underlying interstitial lung disease, being over 65 years old, having high-risk comorbidities, or having an immunosuppressive status. The criteria for inclusion were as follows: a confirmed diagnosis of COVID-19 pneumonia through polymerase chain reaction (PCR) testing, presence of the aforementioned prior and follow-up CT scans, and receipt of at least one dose of vaccination. Therefore, our study included a total of 94 patients (Figure 1). All COVID-19 cases included in this study tested positive for the PCR test.

Data collection

Age, gender, coexisting conditions (hypertension, diabetes, malignant disease, anemia, immunosuppressive diseases, and other disorders), and drugs used were all collect-ed. In addition, the individual's vaccination status, the quantity of doses received, dates of administration, and the producer of the vaccine were all documented. Furthermore, when diagnosed with COVID-19, at the onset of the disease, the hospital laboratory records included the collection of base-line measurements such as hemoglobin (Hb), white blood cell count (WBC), count of platelets (Plt), lymphocyte count, neutrophil count, neutrophil to lymphocyte ratio (NLR), C-reactive protein (CRP), D-dimer, and ferritin levels.

The study included 94 COVID-19 pneumonia patients who were categorized based on the quantity of BioNTech or Sinovac vaccines they received before their first COVID-19 infection. The patients were divided into two groups: those who were incompletely vaccinated (received 1 dose) and those who were completely vaccinated (received 2 doses), with or without additional booster doses (3 doses). The choices of vaccine type were made in our country according to people's preferences, not according to an indication deter-mined by the Turkish Ministry of Health.

COVID-19 diagnosis and severity classification

PCR test results, with a specificity of over 99%, have been widely recognized as the most reliable diagnostic criterion for detecting COVID-19 infection [17]. The index date refers to the date when the initial diagnosis of COVID-19 patients was documented. In addition, we assessed patients based on the extent of their pulmonary COVID-19 infection.

The National Healthcare Commission's Recommendation for the Evaluation and Treatment Plan of COVID-19 Infection categorizes lung COVID-19 infection into three distinct types: Mild to moderate pneumonia characterized by fever, symptoms of respiration, and radiological manifestations. Severe pneumonia is defined by the presence of one or more of the signs that follow: Pulmonary distress is indicated by a respiratory rate (RR) exceeding 30 breaths per minute, a saturation level of oxygen of 93% while at rest, or a ratio of PaO2/FiO2 of 300 mmHg. The condition is considered extremely severe if one or more of the following criteria are met: A respiratory condition that requires the use of mechanical ventilation, shock, especially when combined with additional organ dysfunction, necessitates critical care in the intensive care unit.

Chest CT protocol and image analysis - measurements

The chest CT images were acquired using a multislice-CT scanner (Somatom Force 64, Siemens Healthineers, Germany). After acquiring the scout image, imaging was con-ducted in a direction from the head to the tailbone while the person was supine position. The imaging was done with the following settings: 90/150 Sn kVp, 60 mAs, and a rotation time of 0.33 seconds. Imaging reconstruction was performed with a slice thickness of 1.5 mm in the axial plane. Two radiologists, with 9 and 11 years of experience respectively, collectively assessed the chest CT scans. The chest CT scans were evaluated using a workstation (Syngo.via, Siemens Healthineers, Erlangen, Germany) in order to determine the amount of pulmonary sequelae. The images were opened in the "MM Reading" applica-tion on the workstation, and the boundaries of the sequelae region were determined by selecting "Contour" from the "VOI freehand" tab, and then the data was obtained by calculating the volume with "Create VOI".

All patients in the research had previous chest CT scans acquired prior to the index date and stored in the PACS archive, which revealed no sequelae in the lung parenchymal areas. COVID-19 pneumonia was diagnosed based on the identification of certain abnormalities, such as ground glass opacity and consolidation, on the chest CT scan using the accepted terms for chest imaging established by the Fleischner Society [18]. Specific types of complications were evaluated as pleuroparenchymal linear atelectasis, tractional bronchiectasis, and ground-glass patches typically focused in the peripheral and basal regions of the lung parenchyma [12].

Statistical analysis

The Shapiro-Wilk test was employed for assessing the normality of distributions of continuous variables. The median is the descriptive statistics for continuous data. Numbers and percentiles are used to represent categorical data. The Student's t-test will be employed for comparing normally distributed variables across both groups, whereas the Mann-Whitney U test will be utilized to analyses data that has an irregular distribution. The Chi-square test and, if needed, the Fisher exact test were used to do categorical evaluations. The data was analyzed using SPSS for Windows, version 24.0 (SPSS Inc., Chicago, IL, USA). P-value < 0.05 was considered statistically significant.

Results

Study population

This study includes a cohort of 94 patients diagnosed with COVID-19, consisting of 43 females and 51 males. The age distribution of females ranged from 24 to 63, with a median age of 55. The age distribution of males ranged from 26 to 64, with a median age of 57. The overall median age was found to be 57.

After undergoing inpatient therapy at the hospital, a total of 18 patients diagnosed with severe Covid-19 pneumonia successfully recovered. Additionally, out of the 76 patients diagnosed with mild to moderate COVID-19 pneumonia, 8 required hospitalization. The study population did not have any cases of critically severe COVID-19 pneumonia or fatalities. Table 1 provides an overview of the specific clinical and demographic aspects of the patients.

Out of the total of 94 participants in the trial, 53 individuals were administered Sinovac vaccines while 41 individuals were given BioNTech vaccines. Table 2 shows the dose counts of patients vaccinated with Sinovac and BioNTech.

Table 1. Data analysis of the general characteristics of the patients	
Variables	All population n = 94
Gender, n (%)	
Female	43 (45.7)
Male	51 (54.3)
Age, years	57 (24–64)
Hemoglobin, g/dL	14.1 (10.8–16.7)
Leukocytes, ×103/µL	6.9 (3.92–10.73)
Platelets, ×103/µL	205 (175–304)
Lymphocytes, ×103/µL	1.32 (0.76–1.75)
Neutrophils, ×103/µL	5.04 (2.55–8.56)
NLR	5.42 (2.61–7.78)
CRP, mg/L	46.9 (16–110)
D-Dimer, µg/L)	374 (185–823)
Ferritin, ng/mL	314 (180–659)
Severity of disease, n (%)	
Severe	18 (19.1)
Mild–moderate	76 (80.9)
Data are median (IQR) or number (%). CRP, C-reactive protein; NLR, neutrophil to lymphocyte ratio.	

Table 2. Quantity of vaccine doses for each type		
Vaccine types	Fully Vaccinated (≥ 2 doses) n = 83	Incompletely Vaccinated (1 dose) n = 11
Sinovac - CoronaVac	47 (56.6)	6 (54.5)
BioNTech - BNT162b2	36 (43.4)	5 (45.5)
Data are number (%).		

Relationship between vaccine type, blood parameters and sequelae status

There were no sequelae in 82 patients. The remaining 12 patients had sequelae found on the 1st year control chest CT. 7 of the patients with pulmonary sequelae were in the group vaccinated with Sinovac before the index date, and the other 5 were in the group vaccinated with BioNTech. There was no discernible correlation between the type of vaccine administered and the occurrence of post-COVID pulmonary sequelae ($p > 0.05$).

It was noted that no sequelae developed in any of the patients who received the booster dose (3rd dose) in both vaccine groups.

Table 3 compares the clinical and vaccination characteristics of the patients with either the existence or absence of sequelae. Patients in both groups shared similar age and gender distribution features ($p > 0.05$).

A significant relationship was found between the presence of sequelae and lympho-penia. Patients with pulmonary sequelae had considerably lower lymphocyte counts. Table 4 and Table 5 compare the clinical features of patients in the two groups based on the vaccine types and either the existence or absence of sequelae.

When the blood parameters of patients are investigated by vaccine type, it is clear that CRP and D-Dimer levels, in addition to lymphopenia, are significantly higher in patients having pulmonary sequelae vaccinated with Sinovac.

Correlation with vaccine type and quantity of sequelae

A substantial relationship was discovered between the type of vaccine and the quan-tity of sequelae ($p = 0.005$). In the volume measurements of the sequelae areas observed in the lung parenchyma, the overall median volume value was found to be 136 cm3 (58.4-387.5). While the median volume value of the sequelae areas in the fully vaccinated Sinovac group was 208.4 cm3 (87.5-387.5), it was 85.7 cm3 (58.4-156.1) in the fully vaccinated BioNTech group.

Figure 2 shows chest CT images from a 49-year-old female who received two doses of the BioNTech vaccine.

Figure 3 shows chest CT images of a 55-year-old female who received two doses of the Sinovac vaccine.

Discussion

This study assessed the incidence of lung sequelae following COVID-19 infection using CT imaging in patients previously vaccinated with BNT162b2 or CoronaVac. In addition, a quantitative sequelae evaluation was made between the two groups by measuring the volume of the pulmonary sequelae areas. The most important finding in our study was that the quantity of sequelae in patients who were fully vaccinated with Sinovac and had post-COVID pulmonary sequelae was significantly higher than in those vaccinated with BioNTech.

The Pfizer–BioNTech vaccine is an mRNA-based COVID-19 vaccine. Previous clinical trials have shown that the Pfizer/ BioNTech vaccine is 95% effective at preventing COVID-19 infection. Recent clinical research validates the effectiveness of the BioN-Tech vaccines in preventing infection and demonstrates their efficacy in reducing hospitalizations, admissions to intensive care units, and mortality rates [19, 20]. Furthermore, vaccination not only provides protection against initial infection but also appears to re-duce the occurrence of long-term COVID symptoms and complications in the lungs following reinfection. Multiple studies tend to corroborate this perspective [12, 21].

Table 3. The correlation between the clinical and vaccination characteristics of the patients and the existence or absence of sequelae

Variables	Sequelae exist (n = 12)	No Sequelae (n = 82)	P-value
Gender, n (%)			0.565
Female	5 (41.7)	38 (46.3)	
Male	7 (58.3)	44 (53.7)	
Age, years	55 (34–64)	53 (24–62)	0.349
Hemoglobin, g/dL	14.2 (10.8–15.8)	13.9 (11.5–16.7)	0.280
Leukocytes, ×103/µL	6.54 (3.92–10.73)	7.1 (4.56–9.39)	0.167
Platelets, ×103/µL	198.3 (185.4–304)	214.7 (175–286)	0.274
Lymphocytes, ×103/µL	1.08 (0.76–1.24)	1.44 (1.16–1.75)	< 0.001*
Neutrophils, ×103/µL	4.53 (3.39–8.56)	5.37 (2.55–7.89)	0.154
NLR	4.92 (2.61–6.76)	5.86 (2.91–7.78)	0.099
CRP, mg/L	56 (16–110)	44 (29–103)	0.483
D-Dimer, µg/L	473 (269–823)	351 (185–704)	0.415
Ferritin, ng/mL	396 (180–644)	295 (167–659)	0.269
Severity of disease, n (%)			0.320
Severe	7 (41.7)	11 (13.4)	
Mild–moderate	5 (58.3)	71 (86.6)	
Sinovac, n (%)			< 0.001*
Single dose	3 (42.9)	3 (6.3)	
Two and above	4 (57.1)	43 (93.7)	
Biontech, n (%)			< 0.001*
Single dose	2 (40)	3 (8.3)	
Two and above	3 (60)	33 (91.7)	

Data are median (IQR) or number (%). * p<0.05 indicates statistical significance. CRP, C-reactive protein; NLR, neutrophil to lymphocyte ratio.

Table 4. The relationship between clinical features of patients vaccinated with Sinovac and the possibility of sequelae

Variables	Sequelae exist n = 7	No Sequelae n = 46	P-value
Gender, n (%)			0.328
Female	3 (42.8)	18 (39.1)	
Male	4 (57.2)	28 (60.9)	
Age, years	58 (34–63)	54 (24–62)	0.305
Hemoglobin, g/dL	14.2 (11.5–15.8)	14.3 (11.5–16.1)	0.430
Leukocytes, ×103/µL	6.91 (4.63–10.73)	7.06 (4.81–9.01)	0.372
Platelets, ×103/µL	210.3 (185.4–304)	214.7 (186–280)	0.350
Lymphocytes, ×103/µL	0.91 (0.76–1.05)	1.52 (1.16–1.71)	0.001*
Neutrophils, ×103/µL	4.63 (3.39–8.29)	5.35 (2.55–7.62)	0.115
NLR	5.08 (3.45–6.76)	5.91 (2.91–7.78)	0.109
CRP, mg/L	74 (58–110)	40 (29–90)	< 0.001*
D-Dimer, µg/L	515 (376–823)	326 (195–652)	0.001*
Ferritin, ng/mL	431 (270–644)	315 (167–531)	0.095
Severity of disease, n (%)			0.220
Severe	4 (57.2)	7 (15.2)	
Mild–moderate	3 (42.8)	39 (84.8)	

Data are median (IQR) or number (%). * p<0.05 indicates statistical significance. CRP, C-reactive protein; NLR, neutrophil to lymphocyte ratio.

Table 5. The relationship between clinical features of patients vaccinated with BioNTech and the possibility of sequelae

Variables	Sequelae exist n = 5	No Sequelae n = 36	P-value
Gender, n (%)			0.415
Female	2 (40)	20 (55.6)	
Male	3 (60)	16 (44.4)	
Age, years	51 (42–64)	52 (24–62)	0.526
Hemoglobin, g/dL	13.5 (10.8–14.6)	14 (12.1–16.7)	0.175
Leukocytes, ×103/µL	6.54 (3.92–9.51)	6.86 (4.56–9.39)	0.215
Platelets, ×103/µL	198.3 (185.4–240)	223 (175–286)	0.167
Lymphocytes, ×103/µL	1.08 (0.85–1.24)	1.40 (1.21–1.75)	< 0.001*
Neutrophils, ×103/µL	4.76 (3.75–8.56)	5.17 (2.96–7.89)	0.140
NLR	4.81 (2.61–5.54)	5.56 (3.5–7.41)	0.115
CRP, mg/L	45 (16–81)	52 (36–103)	0.650
D-Dimer, µg/L	384 (269–655)	351 (185–704)	0.635
Ferritin, ng/mL	431 (270–644)	315 (167–531)	0.244
Severity of disease, n (%)			0.195
Severe	3 (60)	4 (11.1)	
Mild–moderate	2 (40)	32 (88.9)	

Data are median (IQR) or number (%). * p<0.05 indicates statistical significance. CRP, C-reactive protein; NLR, neutrophil to lymphocyte ratio.

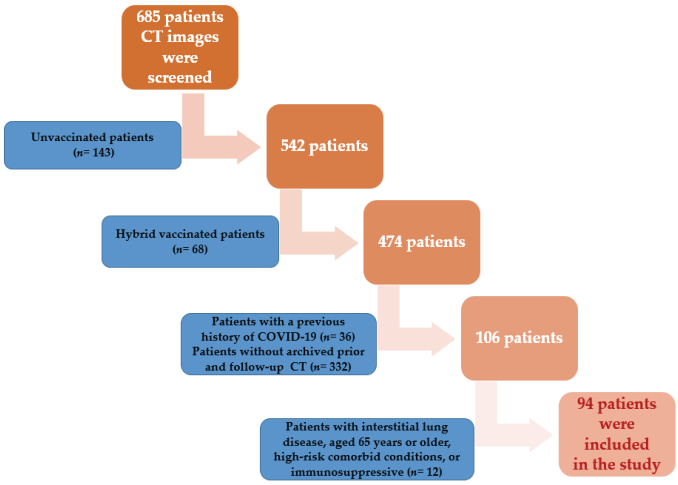

Figure 1. Diagram showing the study population.

CoronaVac is a COVID-19 vaccine that uses an entirely inactive virus. Although it is the most widely utilized COVID-19 vaccine globally, CoronaVac has received little re-search when compared to other vaccines [14]. In previous studies, its effectiveness against SARS-CoV-2 is approaching 95%. Moreover, these vaccines have demonstrated a high level of efficacy in diminishing hospitalizations, admissions to intensive care units, and mortality rates caused by COVID-19. Additionally, they are highly effective in preventing and minimizing long-term complications after infection [2, 13, 22].

After vaccination, cellular and humoral immune responses are established in the body. In the cellular response, the formation of cytotoxic T-lymphocytes occurs, and in the humoral response, B cell maturation takes place in the germinal centers of the lymph nodes [23, 24]. The pathogenic memory B-cell response in SARS-CoV-2, which can be triggered by prolonged autoantibody production in long-term COVID patients, has been held responsible [25, 26]. BNT162b2 significantly enhances SARS-CoV-2-specific binding and neutralizing antibody responses. On the other hand, CoronaVac induces stronger responses from CD4+ and CD8+ T cells compared to BNT162b2 [27, 28]. By inducing the described immune responses, vaccination can prevent organ damage by enabling faster clearance of SARS-CoV-2 and may contribute to the effective clearance of post-acute viral reservoirs [29].

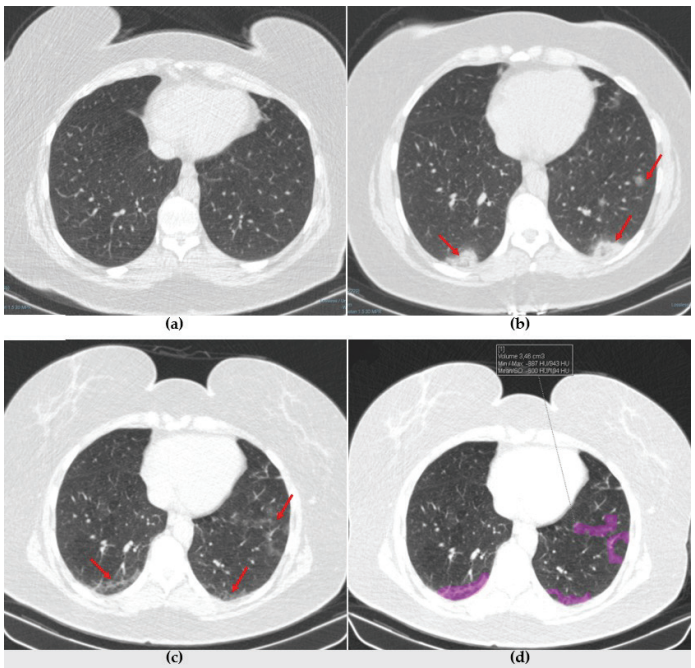

Figure 2. A 49-year-old female COVID-19 patient, vaccinated with two doses of BioNTech vaccine, presenting with dry cough for 1 week. (a) In the axial thorax CT images acquired 6 months before the index date, no infiltration is seen in either lung parenchyma. **(b)** The axial thorax CT

images acquired the index date shows a patchy ground glass opacity (GGO) appearance in the bilateral lower lobes and left upper lobe (red arrows). **(c)** 1 year follow-up axial thorax CT images show that GGO appearance of the bilateral lower lobes is lesser compared to the previous CT scan. Multiple fibrotic parenchymal bands and patchy opacities (red arrows) were found, especially in the anterior basal segment of the left lower lobe. **(d)** The parenchymal volume of this patient with sequelae was computed as 85.7 cm3 based on volume measurements taken in all parts where the sequelae areas were observed.

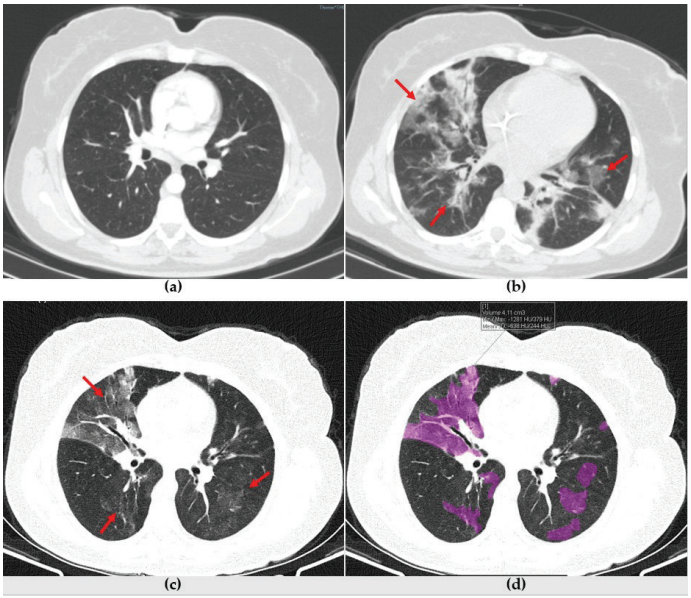

Figure 3. A 55-year-old female COVID-19 patient, vaccinated with two doses of Sinovac vaccine, presenting with fever and dry cough for 4 days. (a) In the axial thorax CT images acquired 8 months before the index date, no infiltration is seen in either lung parenchyma. **(b)** The axial thorax CT images acquired the index date shows a patchy ground glass opacity (GGO) appearance in the bilateral lower lobes, right middle lobe and left upper lobe (red arrows). **(c)** 1-year follow-up axial thorax CT images show that GGO appearance of the bilateral lower lobes and left upper lobe is lesser compared to the previous CT scan. Multiple fibrotic parenchymal bands and patchy opacities (red arrows) were found, especially in the right middle lobe. **(d)** The parenchymal volume of this patient with sequelae was computed as 387.5 cm3 based on volume measurements taken in all parts where the sequelae areas were observed.

In our study, while there was no significant difference in the presence of post-COVID lung sequelae between the two patient groups vaccinated with BioNTech mRNA and Sinovac inactivated virus vaccines, it was observed that the quantity of sequelae in the Sinovac group was significantly higher than the BioNTech group. Moreover, both the basal CRP and D-Dimer values of patients with sequelae in the Sinovac vaccinated group were considerably higher. This situation implies that the protection of the Sinovac vaccine may be insufficient in severe cases.

When we examined the effect of blood parameters on the presence of pulmonary sequelae in the total population, we discovered that only lymphocyte counts could have a predictive effect. Multiple studies have indicated that the lymphocyte count can serve as an indicator of the seriousness of COVID-19 and can be used to predict the occurrence of lung sequelae. According to reports, when the number of lymphocytes decreases, the disease gets more severe and the possibility of sequelae increases [30, 31]. Supporting the literature, we observed lower lymphocyte counts in patients with pulmonary sequelae.

In addition, when the blood parameters of the subgroups according to vaccine types are examined, more significant results are noted on the index date in patients with sequelae in the Sinovac group. Furthermore, elevated levels of CRP and D-Dimer were observed in this group, in addition to lymphopenia. Therefore, blood parameters should be examined more closely when following these cases.

This research examined COVID-19 patients who had different vaccination status and became the first to provide current information about the relationship between the mRNA and inactive viral vaccines as well as the likelihood of developing pulmonary sequelae. An additional benefit of this study is its contribution to the limited body of research comparing these two vaccine types in the literature. Last but not least, this study represents the initial assessment of quantitative sequelae data with CT imaging in addition to sequelae rates following lung infection. Furthermore, the combination of blood tests and imaging findings resulted in a more comprehensive and reliable evaluation.

This study had multiple constraints. To begin with, it is a single-center trial with a small patient population. To corroborate our findings, larger cohort studies from multiple centers are needed. Another issue is that there are studies stating that Hemoglobin and Hematocrit values are effective in predicting the possibility of post-COVID lung sequelae. Unfortunately, we were unable to acquire results on this subject because we could not access these blood parameters of all cases. Similarly, since we did not have access the medical history of all cases, we could not evaluate the effect of comorbidities such as diabetes, hypertension, hyperlipidemia, and coronary artery disease on the sequelae. Furthermore, it is important to note that this study does not provide a comprehensive analysis of symptomatic COVID-19 pneumonia caused by variant virus. This limitation arises from

the fact that not all variants of COVID-19 have been thoroughly characterized, and we lack information regarding the timing of vaccination in relation to the index date for the patients. Future research should concentrate on vaccination prophylaxis against sequalae rates as well as sequalae pathogenesis in various organ systems. Targeted treatment approaches can thus be devised to assure long-term protection.

Conclusion

Our study demonstrated that the type of vaccine has no effect on the prevalence of sequelae. However, the amount of quantitative sequelae is significantly higher in inactivated virus vaccines, and the effect of laboratory parameters on the development of sequelae is more evident in this group.

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Conflicts of Interest

The authors declare they have no conflicts of interest.

Ethics Approval

The study was approved by the the Clinical Research Ethics Committee at Erzincan Binali Yildirim University (Protocol number: EBYU-KAEK-2023-11-002-EC-023567.003 / Date: 02 November 2023).

Informed Consent

Each patient gave written informed consent for the publication of this article using their data.

Availability of Data and Material

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

Authors' contribution

Concept – G.Ç., Design- G.Ç., and K.B.M., Data collection and/or processing - G.Ç., and K.B.M., Analysis and/or interpretation - G.Ç., and K.B.M., Writing – G.Ç., Critical review – K.B.M.. All authors read and approved the final version of the manuscript.

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Research Article

The relationship between leukocyte-based inflammation indices and essential tremor

Lökosit bazlı enflamasyon indeksleri ile esansiyel tremor arasındaki ilişki

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Abstract

Aim: Previous limited studies have indicated that pro-inflammatory cytokines are elevated in patients with essential tremor (ET). This elevation could lead to a more pronounced inflammatory response in these patients. Thus, this study aimed to investigate the relationship between leukocyte-based inflammatory indices and ET.

Material and Methods: In this retrospective study, 103 patients diagnosed with ET between January 2021 and December 2023 were included, along with 103 healthy individuals who were matched by age and gender, participated in check-up programs, and had no other comorbidities. To evaluate tremor severity, the Fahn-Tolosa-Marin (FTM) tremor rating scale was utilized. The leukocyte-based inflammatory indices were calculated as follows: NLR= neutrophils / lymphocytes, PLR = platelets / lymphocytes, systemic immune-inflammation index (SII) = platelets × neutrophils / lymphocytes, and systemic inflammatory response index (SIRI) = neutrophils × monocytes / lymphocytes.

Results: The ET group exhibited higher levels of leukocytes, their subtypes, CRP and leukocyte-based inflammatory indices compared to the control group. Increased CRP (OR= 3.71, $p < 0.001$) and SIRI (OR= 11.73, $p < 0.001$) levels were independent predictors of ET. In predicting ET. SIRI exhibited superior diagnostic performance compared to other inflammatory parameters. The threshold for SIRI levels was set at 7 and above, with a sensitivity of 85.4% and a specificity of 82.5%. There was a positive correlation between SIRI and FTM scores.

Conclusion: Among the leukocyte-based inflammation indices, SIRI demonstrated superior diagnostic performance in predicting ET and was associated with higher tremor severity. This suggests that inflammation may play a potential role in the pathophysiology of ET.

Keywords: essential tremor, inflammation, tremor severity, systemic immune-inflammation index

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Öz

Amaç: Daha önce yapılan sınırlı çalışmalar, esansiyel tremor (ET) hastalarında proinflamatuar sitokinlerin arttığını göstermiştir. Bu artış, bu hastalarda daha belirgin bir inflamatuar yanıtı tetikleyebilir. Bu nedenle, bu çalışma lökosit bazlı inflamasyon indeksleri ile ET arasındaki ilişkiyi araştırmayı amaçladı.

Gereç ve Yöntemler: Bu retrospektif çalışmaya, Ocak 2021 ile Aralık 2023 arasında ET tanısı alan 103 hasta ile yaş ve cinsiyet açısından eşleştirilen, check-up programlarına katılan ve başka komorbiditesi olmayan 103 sağlıklı birey dahil edilmiştir. Tremor şiddetini değerlendirmek için Fahn-Tolosa-Marin (FTM) tremor derecelendirme skalası kullanılmıştır. Lökosit bazlı inflamasyon indeksleri şu şekilde hesaplanmıştır: NLR = nötrofiller / lenfositler, PLR = trombositler / lenfositler, sistemik immün-enflamasyon indeksi (SII) = trombositler × nötrofiller / lenfositler ve sistemik inflamatuar yanıt indeksi (SIRI) = nötrofiller × monositler / lenfositler.

Bulgular: ET grubunda lökosit, alt tipleri, CRP ve lökosit bazlı inflamasyon indeksleri kontrol grubuna göre daha yüksek seviyelerdeydi. Artmış CRP (OR = 3.71, $p < 0.001$) ve SIRI (OR = 11.73, $p < 0.001$) seviyeleri, ET'nin bağımsız öngörücüleri olarak belirlendi. ET'yi öngörmede, SIRI diğer inflamatuar parametrelere göre üstün bir tanısal performans sergilemiştir. SIRI seviyeleri için eşik değer 7 ve üzeri olarak belirlendi ve bu değer %85.4 duyarlılık ve %82.5 özgüllük gösterdi. SIRI ile FTM skorları arasında pozitif bir korelasyon bulundu.

Sonuçlar: Lökosit bazlı inflamasyon indeksleri arasında, SIRI ET'yi öngörmede üstün bir tanısal performans sergilemiş ve daha yüksek tremor şiddeti ile ilişkilendirilmiştir. Bu da inflamasyonun ET'nin patofizyolojisinde potansiyel bir rol oynayabileceğini düşündürmektedir.

Anahtar Kelimeler: esansiyel tremor, inflamasyon, tremor şiddeti, sistemik immün-enflamasyon indeksi

Introduction

Essential tremor is characterized as a "bilateral upper extremity action tremor" and ranks as one of the most prevalent movement disorders affecting adults. Globally, the basic prevalence rates of essential tremor among adults vary between 0.4% and 6%. It is estimated that about 1% of the general population and 4-5% of individuals over the age of 65 are affected by essential tremor [1]. The underlying pathophysiology of essential tremor remains poorly understood. However, there is increasing evidence suggesting that inflammation and neurodegeneration may play roles in the pathophysiology of essential tremor.

Recently, a growing body of research has shown that the clinical presentation of essential tremor encompasses more than just motor symptoms like tremor and gait ataxia. It also includes a range of non-motor features, such as depression, anxiety, cognitive alterations, and sensory changes [2, 3]. Motor and non-motor symptoms manifest in various combinations in essential tremor, contributing to the clinical heterogeneity of the condition [4]. Some researchers report that the diverse clinical features observed in essential tremor resemble those in Parkinson's disease, suggesting that neurodegeneration plays a role in the pathophysiology of essential tremor [5]. It is widely accepted that neuroinflammation plays a role in the pathophysiology of neurodegeneration. However, the extent of its contribution to the progression of neurodegenerative diseases remains a focal point of intensive research, particularly concerning the most prevalent conditions such as Parkinson's disease and Alzheimer's disease [6-8]. It has been reported that pro-inflammatory cytokines are elevated in patients with essential tremor [9]. However, the relationship between blood inflammatory parameters or indices derived from them and essential tremor remains elusive and under-researched [10].

Due to the increase in pro-inflammatory cytokines in patients with essential tremor, we hypothesized that these patients might exhibit a distinct systemic inflammatory response. This study aims to investigate the connection between blood inflammation parameters and essential tremor.

Material and Methods

Following the principles set forth in the Declaration of Helsinki, this single center retrospective study was conducted at the Istanbul Atlas University Medicine Hospital Neurology Clinical from January 2021 to December 2023. The study received approval from the local ethics committee the Research Ethics Committee (Approval Date: 15.02.2023, Decision No: E-22686390-050.99-24274). The local ethics committee waived the requirement of informed consent due to the retrospective nature of the research.

Study population

A total of 173 patients diagnosed with essential tremor were retrospectively examined. The exclusion criteria included: patients over the age of 65, those with a history of surgical intervention in the last year, those with any history of

systemic inflammatory or autoimmune diseases, those with any comorbid conditions (such as Parkinson's disease, heart diseases, thyroid dysfunction, liver diseases, malignancy, renal failure, chronic neurological diseases), those with a history of sepsis, those with a history of anti-inflammatory or chronic corticosteroid medication use, those taking antibiotics, antivirals, antiplatelet agents, anticoagulants, and immunosuppressive agents, those who are pregnant or have given birth in the last 90 days, those with a history of breastfeeding, and those with incomplete clinical data. After this exclusion process, 103 essential tremor patients were enrolled in this study. Additionally, the study included a control group of 103 healthy individuals who were enrolled in and examined through a check-up program, matched with patients with essential tremor in terms of age and gender, and who had no additional comorbidities.

Study protocol

Demographic and clinical data were collected using the hospital's electronic information system and patient files. Venous blood samples, collected after a 12-hour fasting period during outpatient evaluations, were used to analyze biochemical parameters. These samples were processed in a single laboratory, employing the consistent methodology outlined below.

The diagnosis of essential tremor was established by following the diagnostic criteria specified by the Tremor Task Force of the International Parkinson and Movement Disorder Society in their 2018 Criteria [11]. To evaluate tremor severity, the Fahn-Tolosa-Marin (FTM) tremor rating scale was utilized [12]. Severity was determined via dividing the total score by the maximum score. Scores below 50% indicated low severity (encompassing no functional disability and mild/moderate disability), while scores above 50% indicated high severity (including marked and severe disability).

Biochemical analysis

A Cell-Dyn 3700 SL device (Abbott Diagnostics, Chicago, USA) was used to evaluate patients' venous blood samples. Levels of hemoglobin (photometrically), platelet count (impedance method), and C-reactive protein (CRP) (immunoturbidimetric method) were determined. The inflammatory indices were respectively calculated as follows: NLR = neutrophil count / lymphocyte count, PLR = platelet count / lymphocyte count, SII = platelet count × neutrophil count / lymphocyte count, and SIRI = neutrophil count × monocyte count / lymphocyte count.

Statistical analysis

All data were analyzed with IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean (standard deviation [SD]) values while non-normally distributed variables are given as median (25th-75th quartile) values. For comparisons between groups, Student t-test and Mann-Whitney U test were used in line with the normality of the considered distribution. Categorical variables are given as numbers and percentages, and inter-group comparisons were conducted with Chi-square and Fisher exact tests. Spearman correlation analyses were applied to evaluate the relationships between numerical variables. Spearman correlation coefficient of <0.10 were evaluated as negligible correlation, 0.10–0.39 as weak correlation, 0.40–0.69 as moderate correlation, 0.70–0.89 as strong correlation, and 0.90–1.00 as almost perfect very strong correlation [13]. Multivariable logistic regression analysis with the backward Wald method was subsequently performed to identify any possible independent predictors of essential tremor. The receiver operating characteristic (ROC) curve analysis was applied to assess diagnostic performance. Threshold values were determined by the Youden index method. Comparison of the AUC curves was performed with a nonparametric approach using using the theory on generalized U-statistics to generate an estimated covariance matrix previously reported by DeLong et al [14]. Significance was accepted at $P < 0.05$ (*) for all statistical analyses.

Results

The study included 103 control participants (mean age: 46.7±15.7 years) and 103 individuals with essential tremor (mean age: 44.9±15.2 years). The majority of patients with essential tremor had left-hand dominance (81.6%). The proportion of patients with bilateral tremor affecting primarily the head was 39.8%. None of the patients exhibited tremors in the face, tongue, voice, or torso.

In the essential tremor group compared to the control group, the mean leukocyte counts was higher (6.9 ± 1.7 vs. 6.3 ± 1.3 ×103 µL, $p = 0.016$), median neutrophil counts (3.6 vs. 2.9 ×103 µL, $p < 0.001$), mean monocyte counts (0.6 ± 0.2 vs. 0.4 ± 0.1 ×103 µL, $p < 0.001$), and median CRP level (2.9 vs. 1.8 mg/dL, $p < 0.001$), while the median lymphocyte counts was found to be lower (2.2 ± 0.6 vs. 2.4 ± 0.5 ×103 µL, $p = 0.002$). Also, in the essential tremor group, inflammation indices (NLR, PLR, SII, and SIRI) were found to be higher (Table 1). Parameters associated with essential tremor were included in a multiple regression analysis. According to this analysis, increased levels of CRP and SIRI were identified as independent predictors of essential tremor (Table 2).

In predicting essential tremor, the SIRI demonstrated superior diagnostic performance compared to other inflammation parameters (Figure 1) (Table 3). The threshold for SIRI levels was set at 7 and above, with a sensitivity of 85.4% and a specificity of 82.5%. Increased SIRI scores were found to be associated with higher scores on the FTM scale (Table 4).

Table 1. Demographic and laboratory findings.

Variables	Essential tremor n=103	Control n=103	p
Age, years	44.9 ± 15.2	46.7 ± 15.7	0.406
Gender, n (%)			
Female	60 (58.3)	57 (55.3)	0.673
Male	43 (41.7)	46 (44.7)	
Dominant hand, n (%)			
Left	84(81,6)	-	-
Right	19(18,4)	-	
Bilateral tremor, n (%)	41(39,8)	-	-
Hemoglobin, g/dL	13.5 ± 1.9	13.7 ± 1.1	0.384
RBC, ×106 µL	4.7 ± 0.6	4.7 ± 0.5	0.490
Leukocytes, ×103 µL	6.9 ± 1.7	6.3 ± 1.3	0.016*
Lymphocytes, ×103 µL	2.2 ± 0.6	2.4 ± 0.5	0.002*
Neutrophils, ×103 µL	3.6 (2.9-4.8)	2.9 (2.4-3.8)	<0.001*
Monocytes, ×103 µL	0.6 ± 0.2	0.4 ± 0.1	<0.001*
Platelets, ×103 µL	252.3 ± 62.6	252.9 ± 59.3	0.946
MPV, fL	9.8 ± 1.0	9.7 ± 0.7	0.172
PDW, fL	10.9 ± 1.8	10.6 ± 1.0	0.116
CRP, mg/dL	2.9 (2.5-3.4)	1.8 (0.9-2.3)	<0.001*
NLR	1.8 (1.2-2.3)	1.0 (0.9-1.6)	<0.001*
PLR	119.4 (92.3-154.3)	95 (90.2-122.2)	0.001*
SII	382.2 (294.5-625)	260.8 (233.4-450.4)	<0.001*
SIRI	1.1 (0.8-1.7)	0.5 (0.1-0.7)	<0.001*

Data are mean ± standard deviation or median (IQR), or number (%). *p<0.05 indicates statistical significance. Abbreviations: RBC, red blood cells; MPV, mean platelet volume; PDW, platelet distribution width, CRP, C-reactive protein; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index

Table 2. Independent predictors of essential tremor.

Variables	Univariable Regression			Multivariable Regression		
	OR	95% CI	p	OR	95% CI	p
CRP	2.84	2.05 – 3.94	<0.001*	3.71	2.37 – 5.81	<0.001*
SII	1.04	1.02 – 1.06	<0.001*	-	-	-
SIRI	19.3	7.89 – 47.22	<0.001*	38.52	11.73 – 126.43	<0.001*
				Nagelkerke R^2= 0.54		

The effects of age and gender were adjusted in the regression analysis. *p<0.05 indicates statistical significance. Abbreviations: CI, confidence interval; CRP, C-reactive protein; OR, odds ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index.

Table 3. Diagnostic performance of inflammatory parameters and indices for predicting essential tremor.

Variables	AUC±SE	95% CI	Sens. (%)	Spec. (%)	Threshold
Leukocytes	0.557 ± 0.04	0.479 - 0.636	39.8	83.5	7.0 ×103 µL
Lymphocytes	0.402 ± 0.04	0.325 - 0.479	6.8	100.0	3.2 ×103 µL
Neutrophils*	0.686 ± 0.04	0.614 - 0.759	76.7	57.3	2.9 ×103 µL
Monocytes*	0.825 ± 0.03	0.768 - 0.882	77.7	84.5	0.5 ×103 µL
Platelets	0.499 ± 0.04	0.420 - 0.579	83.5	32.0	208 ×103 µL
NLR*	0.733 ± 0.03	0.665 - 0.801	90.3	52.4	1.1
PLR*	0.629 ± 0.04	0.553 - 0.705	45.6	82.5	123.8
SII*	0.729 ± 0.03	0.660 - 0.798	90.3	62.1	273.6
SIRI*	0.849 ± 0.03	0.796 - 0.903	85.4	82.5	0.7
CRP*	0.795 ± 0.03	0.734 - 0.857	79.6	77.7	2.4 mg/dL

*p<0.05 indicates statistical significance. Abbreviations: CRP, C-reactive protein; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; Sens, sensitivity; SII, systemic immune-inflammation index; Spec, specificity; SIRI, systemic inflammatory response index.

Table 4. Demographic characteristics of essential tremor patients according to quartile of systemic inflammatory response index (SIRI).

Variables	SIRI				p
	Q1	Q2	Q3	Q4	
	n=26	n=27	n=25	n=25	
Age, years	43.0 (27.5 - 52.8)	48.0 (27.5 - 57.0)	47.0 (28.0 - 60.0)	51.0 (38.0 - 64.0)	0.227
Gender, n (%)					
Female	13 (50.0)	17 (63.0)	12 (48.0)	18 (72.0)	0.262
Male	13 (50.0)	10 (37.0)	13 (52.0)	7 (28.0)	
Dominant hand, n (%)					
Left	18 (69.2)	24 (88.9)	21 (84.0)	21 (84.0)	0.285
Right	8 (30.8)	3 (11.1)	4 (16.0)	4 (16.0)	
Bilateral tremor, n (%)	10 (38.5)	11 (40.7)	9 (36.0)	11 (44.0)	0.477
FTMS scale	11.0 (11.0 - 12.0)	12.0 (11.0 - 19.0)	14.0 (10.0 - 18.0)	20.0 (18.0 - 22.0)	<0.001*

Data are mean ± standard deviation or median (IQR), or number (%). *p<0.05 indicates statistical significance. Abbreviations: FTMS, Fahn-Tolosa-Marin tremor rating scale.

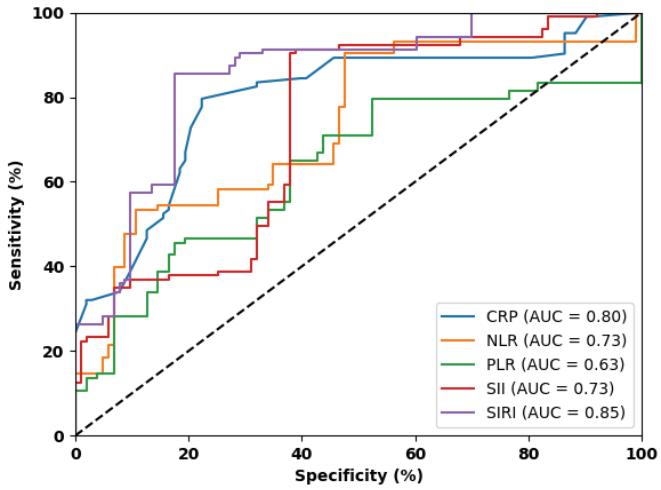

Figure 1. Diagnostic performance of leukocyte-based inflammation indices for predicting essential tremor.

Discussion

To the best of our knowledge, this study is among the few that investigate the connection between essential tremor and leukocyte-driven inflammatory indices. This study also marks the first time that the connection between SII, SIRI, and essential tremor has been evaluated. In patients with essential tremor, leukocyte-based inflammatory indices were elevated, and SIRI was identified as an independent predictor. Furthermore, SIRI surpassed other inflammatory markers in diagnostic performance. An increased SIRI levels correlated with increased FTM scores.

Inflammation, a fundamental biological response to harmful stimuli, has been increasingly recognized in various neurological disorders, suggesting a possible similar impact in essential tremor. Research has demonstrated that individuals with Parkinson's disease exhibit elevated levels of interleukin-8 (IL-8) in their serum. Moreover, there is an observed association between the heightened levels of IL-8 and the severity of clinical symptoms in Parkinson's disease. Specifically, those with the highest serum IL-8 concentrations experience the greatest impairment in daily functioning due to the disease [15]. One significant study explored the relationship between various serum inflammation markers such as interleukin-1β, interleukin-6, interleukin-8, interleukin-10, and tumor necrosis factor-α, and clinical features of essential tremor like tremor severity, cognitive decline, and depression. The aim was to identify any direct correlations between these markers and the clinical manifestations of essential tremor [8]. It has been demonstrated that pro-inflammatory cytokines such as IL-6 are elevated in patients with essential tremor [16]. In an Essential Tremor rat model, it has been shown that Dapagliflozin suppresses the inflammatory cascade and mimics neuronal damage through triggering the LKB1/p-AMPK/GABA B R2 signaling pathway [17]. Additionally, IL-6 has the potential to modulate the AMPK signaling pathway [18]. These findings support the possibility that inflammation and the inflammatory response triggered by immune cells may play a role in the pathogenesis of essential tremor.

Protein heteromers of neutrophil and platelet cells promote monocyte recruitment [19]. Moreover, neutrophils have the potential to modulate macrophages to the anti-inflammatory phenotype, while platelets can affect neutrophil functions [20]. Additionally, neutrophils can release reactive oxygen species (ROS), granular components, and pro-inflammatory mediators [21]. It is suggested that ROS may play a role in the pathogenesis of essential tremor [22]. Additionally, genes

such as APOE, SENP6, and ZNF148 have been found to be differentially expressed in patients with essential tremor [23]. It is also suggested that this genes may regulate ROS and neutrophil functions [24-26]. In patients with essential tremor, leukocytes and their subtypes show significant differences. These findings support the potential role of the immune system in the pathogenesis of essential tremor.

Our study builds upon previous findings that inflammation might influence the neurodegenerative process seen in essential tremor. The recruitment of monocytes facilitated by protein heteromers of neutrophil and platelet cells [27] and the modulatory effects of neutrophils on macrophages to adopt an anti-inflammatory phenotype [28], are examples of potential mechanisms. Furthermore, the role of ROS and cytokines such as IL-6, which were found to be elevated in essential tremor patients, suggests an inflammatory cascade that could exacerbate or contribute to the pathophysiology of essential tremor [12]. A previous study reported that levels of NLR and PLR did not differ between patients with essential tremor and a control group [10]. However, there is a lack of studies that thoroughly evaluate blood inflammation parameters in detail. Inflammatory indices such as CRP, NLR, PLR, SII, and SIRI were consistently higher in ET patients, which corresponds with emerging literature suggesting a pathological link between inflammation and essential tremor [29]. Among these, SIRI emerged as a robust independent predictor of essential tremor, providing a potential new avenue for diagnostic improvement in clinical settings. The utility of SIRI in diagnosing essential tremor was supported by its superior performance in ROC curve analysis, distinguishing it from other inflammatory markers.

The clinical implications of our findings extend beyond mere diagnosis, suggesting that inflammatory markers could also serve as therapeutic targets in essential tremor. Interventions that modulate inflammation, such as the use of anti-inflammatory drugs or lifestyle modifications aimed at reducing systemic inflammation, could potentially alleviate the symptoms or slow the progression of essential tremor. This approach is supported by studies in other neurodegenerative disorders where anti-inflammatory treatments have shown promise in mitigating disease [30]. Therefore, identifying patients with elevated inflammatory markers could not only help in earlier and more accurate diagnosis but also tailor more specific anti-inflammatory therapeutic strategies that may be beneficial in managing essential tremor. Moreover, the interrelation between inflammation and essential tremor provides a compelling argument for the role of the peripheral immune system in central nervous system disorders. The cross-talk between peripheral inflammation and central neurodegeneration might involve complex biochemical pathways that include cytokine signaling and immune cell activation, which can subsequently affect neuronal function and health. Understanding these pathways in greater detail could offer new insights into the etiology of essential tremor and other similar movement disorders, potentially leading to breakthroughs in how these conditions are treated

Our study has several limitations that should be considered. Initially, the low sample size and the single-center retrospective nature were significant limitations. Second, cytokines or chemokines that may play a role in leukocyte trafficking were not analyzed. Evaluation of subtypes of leukocytes by flow cytometry analysis may be more revealing in the development of essential tremor. While our study focused on broad leukocyte-based inflammation indices, flow cytometry analysis of leukocyte subtypes could offer more detailed insights into immune cell involvement in essential tremor. Identifying specific immune cell subtypes may reveal key differences in systemic inflammatory responses during the progression of essential tremor. Evaluations of these factors in future studies might further illuminate the role of systemic inflammatory indices differing throughout the pathogenesis in cases of essential tremor.

Conclusion

The findings gathered from our retrospective study indicates a pronounced inflammatory component in essential tremor patients. This study has highlighted the potential role of systemic inflammation in the pathogenesis of essential tremor, with significant associations between elevated inflammatory markers and the severity of the condition. The novel inflammatory marker SIRI, in particular, presents as a promising diagnostic tool with potential utility in the clinical assessment of essential tremor.

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Conflicts of Interest

The authors declare they have no conflicts of interest.

Ethics Approval

The study was performed in accordance with the Declaration of Helsinki, and was approved by the Istanbul Atlas University Medicine Hospital Clinical Research Ethics Committee (Date: 15.02.2023, Decision No: E-22686390-050.99-24274).

Informed Consent

The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

Availability of Data and Material

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

Authors' contribution

Concept – D.A.Ü., Design – D.A.Ü., Supervision – D.A.Ü, Data collection and/or processing – D.A.Ü. and B.D., Analysis and/or interpretation – D.A.Ü. and B.D., Writing – D.A.Ü., Critical review- B.D. All authors read and approved the final version of the manuscript.

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Research Article

The temporal changes in mean platelet volume after bariatric surgery

Bariatrik cerrahi sonrası ortalama trombosit hacmindeki zamansal değişiklikler

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Abstract

Aim: Studies on obese individuals have proposed a correlation between weight loss and variations in mean platelet volume (MPV). Therefore, this study aimed to examine the changes in MPV in morbidly obese patients who underwent weight loss via bariatric surgery.

Material and Methods: A total of 328 morbidly obese patients who underwent sleeve gastrectomy (morbidly obese group) and were retrospectively evaluated from January 2010 to November 2014. The control group consisted of 53 non-obese patients who had laparoscopic cholecystectomy. Body mass index values and MPV values at preoperative (baseline), postoperative 1st month, 3rd month, and 12th month for both groups were documented.

Results: The baseline MPV values were comparable between morbidly obese group and control group (8.8 ± 1.8 vs. 8.6 ± 1.2, p = 0.283). In control group, there was no significant change in MPV levels during the 12-month follow-up. In morbidly obese group, mean MPV levels at the 1st and 3rd months post-surgery were similar, showing an increase compared to baseline levels. By the 12th month, mean MPV levels tended to decrease, becoming comparable to baseline values.

Conclusion: MPV levels increased in the early postoperative period following sleeve gastrectomy, they returned to baseline by the 12th month. These findings suggest that weight loss from bariatric surgery may influence MPV levels, but this effect normalizes over time.

Keywords: bariatric surgery, sleeve gastrectomy, mean platelet volume, obesit

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Öz

Amaç: Obez bireyler üzerinde yapılan çalışmalar, kilo kaybı ile ortalama trombosit hacmi (MPV) değişiklikleri arasında bir ilişki olduğunu öne sürmüştür. Bu nedenle, bu çalışma, bariatrik cerrahi ile kilo kaybı yaşayan morbid obez hastalarda MPV'deki değişiklikleri incelemeyi amaçladı.

Gereç ve Yöntemler: Ocak 2010 ile Kasım 2014 tarihleri arasında sleeve gastrektomi yapılan toplam 328 morbid obez hasta (morbid obez grup) retrospektif olarak değerlendirildi. Kontrol grubu, laparoskopik kolesistektomi geçiren 53 obez olmayan hastadan oluştu. Her iki grup için preoperative (bazal), postoperatif 1. ay, 3. ay ve 12. ayda vücut kitle indeksi ve MPV değerleri kaydedildi.

Bulgular: Bazal MPV değerleri, morbid obez grubu ile kontrol grubu arasında benzerdi (8.8 ± 1.8 vs. 8.6 ± 1.2, p = 0.283). Kontrol grubunda, 12 aylık takip süresince MPV seviyelerinde anlamlı bir değişiklik gözlenmedi. Morbid obez grubunda, cerrahi sonrası 1. ve 3. ayda ortalama MPV seviyeleri benzer olup, bazal seviyelere göre artış gösterdi. 12. ayda ise ortalama MPV seviyeleri azalma eğilimi göstererek, bazal değerlere benzer hale geldi.

Sonuçlar: MPV seviyeleri, sleeve gastrektomi sonrası erken postoperatif dönemde artış gösterdi, ancak 12. ayda başlangıç seviyelerine döndü. Bu bulgular, bariatrik cerrahi ile kilo kaybının MPV seviyelerini etkileyebileceğini, ancak bu etkinin zamanla normale döndüğünü göstermektedir.

Anahtar Kelimeler: bariatrik cerrahi, sleeve gastrektomi, ortalama trombosit hacmi, obezite

Introduction

Platelets are circulating, disc-shaped anucleate particles measuring 1-2 µm in size, derived from megakaryocytes with a lifespan of 8-10 days. The main role of plateletes is to maintain the integrity of blood vessels through adequate hemostasis and thrombosis [1]. The size and hemostatic potential of circulating platelets are different. When activated, platelets undergo a disc-to-sphere transformation, and reticulated platelets—larger and younger—emerge, leading to an increase in platelet size [2]. These younger larger platelets are metabolically and enzymatically more active and have greater prothrombotic potential than smaller platelets [3]. Platelets with large volume, containe more granules and produce greater amounts of vasoactive and prothrombotic factors such as thromboxane A2, platelet factor 4, beta-thromboglobulin, and serotonin [4].

Platelet size, measured as mean platelet volume (MPV), is a marker of platelet function and is positively associated with indicators of platelet reactivity [5]. In addition to increased MPV, the proportion of reticulated platelets has also been suggested as a marker of increased platelet turnover [6]. An increased in the MPV level is related to hyperaggregability and a shortened time of coagulation [7]. Elevated MPV plays a pivotal role in the pathogenesis of atherothrombosis and cardiovascular outcomes [8].

Obese patients often have elevated MPV levels, making them a risk group for thrombosis [9-12]. There are also studies that suggest either no relationship or a negative correlation between BMI and MPV levels [13-16]. Likewise, conflicting results have been reported in the few studies examining the impact of bariatric surgery on MPV levels, with some studies showing an increase, others showing a decrease, or no change in MPV post-surgery [17, 18]. Therefore, this study aimed to examine the changes in MPV in morbidly obese patients who underwent weight loss via bariatric surgery, addressing the gap in the literature on the impact of weight reduction on platelet function and the inconsistent findings in previous research.

Material and Methods

Patients who underwent bariatric surgery at the Fatih Sultan Mehmet Training and Research Hospital General Surgery Clinic between January 2010 and January 2014 were retrospectively enrolled in this study. The study received the Fatih Sultan Mehmet Training and Research Hospital Clinical Research Ethics Committee approval (Date: 27.10.2014, Decision No: 2014/9) and was conducted in compliance with the relevant ethical guidelines and the Declaration of Helsinki (2013 Brazil revision). The local ethics committee waived the requirement of informed consent due to the retrospective nature of the research.

Study population

A total of 328 morbidly obese patients who underwent sleeve gastrectomy (morbidly obese group) during the study period were retrospectively evaluated. Additionally, 53 non-obese

without any comorbidities who underwent laparoscopic cholecystectomy were included as a control group. All patients met the indications for bariatric surgery according to the 2006 guidelines of the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) [19]. The inclusion criteria for the study were patients aged 18-60 years, with a BMI ≥ 40 kg/m^2 or a BMI of 35-40 kg/m^2 with comorbidities (such as metabolic diseases, cardiovascular diseases, respiratory diseases, joint diseases, psychological problems related to obesity), for whom weight loss achieved through surgical methods was expected to have a positive impact on these issues. Patients with a history of kidney disease, thyroid disease, chronic infectious disease, malignancy or renal or hepatic dysfunction, women who were pregnant, those using steroids or other immunosuppressive therapies, those with a BMI less than 35 kg/m^2, those with documented surgical histories, those who encountered postoperative complications, those who missed their postoperative follow-ups, and those with missing data were excluded from the study. No patients underwent any other bariatric surgery during the follow-up.

Study protocol

The hospital's electronic information system and patient files were used to gather demographic and clinical data. For the obese group, clinical parameters at preoperative (baseline), postoperative 1st month, 3rd month, and 12th month for both groups were documented, while for the control group, they were evaluated at baseline and postoperative 12th month. All samples were analyzed in a single laboratory using the same methodology as described below.

Laboratory parameters

All samples were analyzed in the same laboratory, complete blood count were determined using a Sysmex XN-1000 (Sysmex Corporation, Kobe, Japan) analyzer. Biochemical parameters were analyzed using venous blood samples collected during outpatient evaluations after a 12-hour fasting period. Patients who underwent sleeve gastrectomy were subdivided into nondiabetic, prediabetic and diabetic subgroups according to HbA1c value (HbAc1<5.7; 5.7-6.4 and >6.5 respectively).

Statistical analysis

All data were analyzed with IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean and standard deviation (SD) values while non-normally distributed variables are given as median (min-max). For comparisons between groups, Student T-test and Mann-Whitney U test for two group and ANOVA test and Kruskal-Wallis-H test for three group were used in line with the normality of the considered distribution. Categorical variables are given as numbers and percentages, and inter-group comparisons were conducted with Chi-square and Fisher exact tests. Changes in MPV levels during the follow-up period were assessed using the paired sample t-test or repeated measures ANOVA. Pearson or Spearman correlation analyses were applied to evaluate the relationships between numerical variables, depending on the normality of the distribution. Significance was accepted at $P < 0.05$ (*) for all statistical analyses.

Results

The mean age was similar between the morbidly obese group and the control group (35.9 ± 9.5 vs. 36.3 ± 7.2, p = 0.780). The ratio of female was higher in the morbidly obese group compared to control group (82% vs %22.6, p = 0.001). The baseline MPV values were comparable between morbidly obese group and control group (8.8 ± 1.8 vs. 8.6 ± 1.2, p = 0.283). The demographic and laboratory findings of study population are shown in Table 1.

Table 1. Demographic and laboratory findings of study population.

Variables	Morbidly obese group n = 328	Control group n = 53	P-value
Age, years	35.9 ± 9.5	36.3 ± 7.2	0.780
Gender, n (%)			
Male	59 (18.0)	41 (77.4)	0.001*
Female	269 (82.0)	12 (22.6)	
Weight, kg	127.6 ± 18.5	74.0 ± 9.6	<0.001*
BMI, kg/m2	46.4 ± 6.4	26.2 ± 2.7	<0.001*
HbA1c, %	6.0 ± 0.3	5.0 ± 0.3	<0.001*
MPV, fL	8.6 ± 1.2	8.8 ± 1.8	0.283

Data are mean ± standard deviation or number (%). *p<0.05 indicates statistical significance. Abbreviations: BMI, body mass index; HgA1c, Hemoglobin A1c; MPV, mean platelet volume.

BMI levels significantly decreased in morbidly obese patients following sleeve gastrectomy across all follow-up periods (Baseline: 46.4 ± 6.4 vs. 1st month: 41.6 ± 6.3 vs. 3rd month 38.6 ± 6.4 vs. 12th month: 32.8 ± 6.8, p < 0.001) (Table 2).

In control group, there was no significant change in MPV levels during the 12-month follow-up. In morbidly obese group, mean MPV levels at the 1st and 3rd months post-surgery were similar, showing an increase compared to baseline levels. At the 12th month, mean MPV levels tended to decrease, becoming comparable to baseline values (Figure 1) (Table 3).

Table 2. Changes in BMI levels in morbidly obese patients after sleeve gastrectomy.

Follow-up time	BMI	P-value
Baseline	46.4 ± 6.4 bcd	<0,001*
1 month	41.6 ± 6.3 acd	
3 months	38.6 ± 6.4 abd	
12 months	32.8 ± 6.8 abc	

Data are mean ± standard deviation. *p<0.05 indicates statistical significance. a vs. baseline, b vs. 1 months, c vs. 3 months, d vs. 12 months. Abbreviations: BMI, body mass index

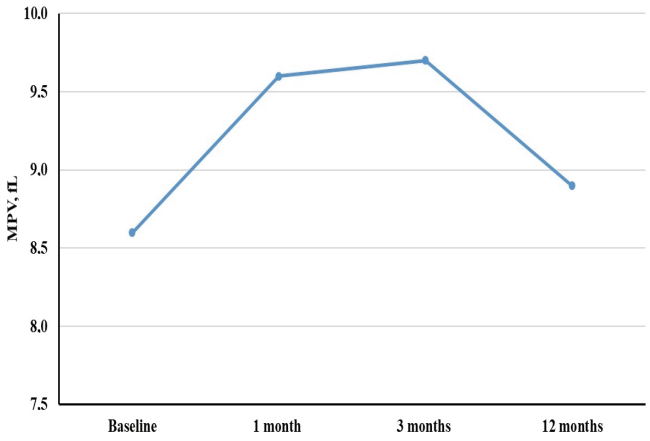

Figure 1. Postoperative variations in MPV levels among morbidly obese patients.

In morbidly obese patients, there was no significant association between baseline BMI and baseline MPV levels. A negative correlation was found between the change in MPV levels and the change in BMI levels at the 1st month ($r = -0.298$; $p = 0.008$) and 3rd month ($r = -0.307$; $p < 0.001$) after surgery. A positive correlation was found between the change in BMI levels and MPV levels at the 12th month ($r = 0.268$; $p = 0.025$)

Discussion

The main findings of this study are as follows: 1) An increase in MPV levels was observed in the short term after sleeve gastrectomy in morbidly obese patients, which negatively correlated with BMI reduction. 2) At the 12th month post-surgery, a decrease in MPV levels was observed, which showed a positive correlation with decreased BMI levels.

In a study conducted by Kutlutürk et al. on 205 morbidly obese patients who underwent laparoscopic sleeve gastrectomy, it was reported that platelet counts decreased, while MPV levels increased during the 6-month after sleeve gastrectomy [18]. In a study by Aykota et al. on 252 morbidly obese patients who underwent laparoscopic sleeve gastrectomy, the patients were followed for 12 months, and similar results were reported [20]. Raoux et al. investigated changes in platelet counts and MPV following bariatric surgery in 128 obese patients [17]. In their study, 90 patients underwent Roux-en-Y gastric bypass surgery, while 38 patients had sleeve gastrectomy. In their study, they reported that MPV increased at the 3rd and 6th months across the entire population and returned to baseline levels by the 12th month. Additionally, they found no significant difference in MPV variations between the two surgical groups [17]. In this study, MPV levels reached their peak at the 1st and 3rd months following sleeve gastrectomy, but were similar to baseline levels over the 12-month period.

Previous studies have reported conflicting results regarding the relationship between weight loss and MPV levels [20-24]. These conflicting results may be attributed to differences in study design, patient populations, or the length of follow-up periods. Variations in the timing of MPV measurements, the degree of weight loss, and the presence of comorbid conditions could also contribute to these discrepancies. Kutlutürk et al. have reported that the increase in MPV levels after LSG was not correlated with a decrease in BMI [18]. Raoux et al. have reported that changes in MPV are correlated with weight loss, especially during rapid weight loss [17]. In the present study, although there was a decrease in BMI levels in the short term following sleeve gastrectomy, MPV levels increased. On the other hand, by the 12th month post-surgery, both BMI and MPV levels had significantly decreased. This could be associated with some postoperative factors. Firstly, the rapid restriction of gastric capacity and loss of appetite after surgery prevent patients from maintaining proper nutrition [25, 26]. It was reported that calorie intake was 30% lower in postoperative 6 weeks, 16% in 1 year and 9% in 2 years compared to preoperative [27]. In a study assessing the impact of various weight loss therapies on MPV, patients followed either a low-calorie diet or a nutritionally

Table 3. Postoperative MPV change in morbidly obese group and control group.

Groups / MPV levels	Baseline	1 month	3 months	12 months	P-value
Morbidly obese	8.6 ± 1.2 bc	9.6 ± 1.4 ad	9.7 ± 1.6 ad	8.9 ± 1.2 bc	<0.001*
Control	8.8 ± 1.8	-	-	8.9 ± 1.6	0.730

Data are mean ± standard deviation. *p<0.05 indicates statistical significance. a vs. baseline, b vs. 1 months, c vs. 3 months, d vs. 12 months. Abbreviations: MPV, mean platelet volume.

complete very low-calorie diet (VLCD) for 8 weeks, followed by a 40-week maintenance period. In both groups, MPV temporarily increased during the 8-week diet phase. By the end of the 48 weeks, MPV had returned to baseline levels. The VLCD group exhibited a smaller change in MPV. However, it was emphasized that there is no relationship between the decrease in MPV and weight loss [28]. This suggests that caloric restriction and fasting may temporarily alter platelet activity and function, possibly influencing MPV levels. Nutritional deficiency has been reported to cause autophagy in platelets, both in animal studies and in humans [29]. Caloric restriction activates autophagy, a catabolic process that helps platelets maintain their function under nutrient-limited conditions by recycling damaged cellular components. This autophagy mechanism plays a crucial role in platelet survival, particularly during periods of fasting or nutritional deficiency. It may also explain the changes in MPV observed during the postoperative period following bariatric surgery, when calorie intake is significantly restricted. On the other hand, thrombocytopenia is a common finding in anorexia nervosa and it has been shown to increase the platelet distribution width, which is anisocytosis indicator [30].

In our study, the increase in MPV peaked between the 1st and 3rd months post-surgery, when calorie intake was highly restricted and weight loss was at its fastest. Another factor influencing the MPV trajectory in patients undergoing sleeve gastrectomy could be ghrelin [31, 32]. Ghrelin is a gut hormone that is mainly secreted by the stomach cell (and other cells) to increase appetite and energy balance. The acetylated form of ghrelin (AG) is known for its cardioprotective, anti-platelet, and anti-thrombotic properties [33]. During sleeve gastrectomy, a significant portion of the stomach, including the ghrelin-producing cells in the fundus, is removed, leading to a substantial decrease in circulating AG levels [34, 35]. While this reduction aids in weight loss, it may increase the risk of platelet aggregation and thrombosis due to its impact on platelet metabolism [33]. The postoperative decrease in platelet count and the negative correlation between platelet count and MPV suggest that younger platelets are in circulation [18, 24].

The current study had several important limitations. The study primarily had a single-center, retrospective design and involved a comparatively small cohort of subjects. It was based on a single-center, retrospective design. Although the sample size was similar to or relatively larger than previous studies, the follow-up period for patients was limited to 1 year. Additionally, our study only examined MPV levels. Changes in platelet count or its indices were not evaluated.

Conclusion

The sleeve gastrectomy significantly affects MPV values, with these changes closely associated with BMI reductions. MPV may serve as a useful biomarker for monitoring postoperative metabolic adjustments and potential thrombosis risk in morbidly obese patients.

Funding

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Conflicts of Interest

The authors declare they have no conflicts of interest.

Ethics Approval

The study was performed in accordance with the Declaration of Helsinki, and was approved by the Fatih Sultan Mehmet Training and Research Hospital Clinical Research Ethics Committee(Date: 27.10.2014, Decision No: 2014/9).

Informed Consent

Informed consent was obtained from all patients.

Availability of Data and Material

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

Authors' contribution

Concept – S.A.K. and A.Ö, Design- S.A.K. and A.Ö; Data collection and/or processing - S.A.K., A.B.K., Y.G., N.O., and A.Ö; Analysis and/or interpretation - S.A.K., A.B.K., Y.G., N.O., and A.Ö; Writing – S.A.K., Critical review- A.B.K., Y.G., N.O., and A.Ö. All authors read and approved the final version of the manuscript.

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Research Article

Factors associated with abnormal dimercaptosuccinic acid (DMSA) renal scan findings in children with vesicoureteral reflux

Vezikoüreteral reflülü çocuklarda anormal dimercaptosüksinik asit (DMSA) renal tarama bulguları ile ilişkili faktörler

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ABSTRACT

Aim: This study aimed to investigate the association between abnormal dimercaptosuccinic acid (DMSA) scan results and demographic factors, vesicoureteral reflux (VUR) severity and laterality, as well as the presence of urinary tract infections (UTIs) in children diagnosed with VUR.

Material and Methods: A retrospective analysis was conducted on 39 children diagnosed with VUR. Data included age, gender, VUR grade, the presence of bilateral VUR, and UTI frequency. DMSA scans were used to assess renal scarring. Statistical comparisons were made between patients with normal and abnormal DMSA results to identify significant predictors of renal damage.

Results: The mean age of the children was 30 months, with 82% being female. VUR Grade III and above was significantly associated with abnormal DMSA findings (81.5% vs. 50%, $p = 0.046$). However, no significant difference was observed in the frequency of bilateral VUR between groups (33.3% vs. 41.7%, $p = 0.618$). Although patients with abnormal DMSA findings had a higher incidence of UTIs, this difference was not statistically significant (63.0% vs. 33.3%, $p = 0.090$).

Conclusion: While higher VUR grades were related to abnormal DMSA results, there was no significant statistical association with bilateral VUR or UTIs. These findings suggest that the severity of VUR may be a more important predictor of kidney damage.

Keywords: Vesicoureteral reflux, DMSA scan, urinary tract infections, renal scarring

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ÖZ

Amaç: Bu çalışmada, vezikoüreteral reflü (VUR) tanısı almış çocuklarda anormal dimercaptosüksinik asit (DMSA) tarama sonuçları ile demografik faktörler, VUR şiddeti ve lateralitesine ek olarak idrar yolu enfeksiyonu (İYE) varlığı arasındaki ilişkinin araştırılması amaçlandı.

Gereç ve Yöntemler: VUR tanısı alan 39 çocuk üzerinde retrospektif bir analiz yapıldı. Veriler, yaş, cinsiyet, VUR derecesi, bilateral VUR varlığı ve İYE sıklığını içeriyordu. DMSA taramaları böbrek skarlarını değerlendirmek için kullanıldı. Anormal ve normal DMSA sonuçları olan hastalar arasında istatistiksel karşılaştırmalar yapıldı.

Bulgular: Çocukların ortalama yaşı 30 ay olup, %82'si kızlardan oluşmaktaydı. VUR derecesi III ve üzeri olan hastalarda anormal DMSA bulguları anlamlı şekilde daha yüksek bulundu (%81,5'e karşı %50, p = 0,046). Ancak, gruplar arasında bilateral VUR sıklığı açısından anlamlı bir fark bulunmadı (%33,3'e karşı %41,7, p = 0,618). Anormal DMSA bulguları olan hastalarda İYE sıklığı daha yüksek olmasına rağmen, bu fark istatistiksel olarak anlamlı değildi (%63,0'a karşı %33,3, p = 0,090).

Sonuç: Yüksek VUR dereceleri anormal DMSA sonuçları ile anlamlı bir ilişki göstermektedir. Ancak, bilateral VUR veya İYE sıklığı ile istatistiksel olarak anlamlı bir ilişki gözlenmemiştir. Bulgular, böbrek hasarının ana belirleyicisinin VUR şiddeti olabileceğini göstermektedir.

Anahtar kelimeler: vezikoüreteral reflü, dimercaptosüksinik asit taraması, idrar yolu enfeksiyonları, böbrek skarı

Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) encompass a wide range of disorders, including disrupted embryonic migration of the kidneys, as well as malformations in the lower urinary system, the urine collecting system, or the development of the renal parenchyma [1]. These anomalies represent a significant cause of chronic kidney disease (CKD) and end-stage renal disease in children, accounting for nearly 30 to 50% of pediatric CKD cases [2]. The monitoring and management of these conditions in pediatric nephrology are critical to improving long-term health outcomes for affected children.

Vesicoureteral reflux (VUR) is a major cause of CAKUT, characterized by the backward flow of urine from the bladder to the ureters and kidneys [3, 4]. It can lead to recurrent urinary tract infections (UTIs) and kidney scarring, especially in high-grade cases [1, 5]. VUR severity and its complications are influenced by several factors, including the grade of reflux, presence of bladder dysfunction, and frequency of UTIs [6, 7]. Dimercaptosuccinic acid (DMSA) renal scans play a crucial role in detecting renal scarring and functional impairment, particularly in children with recurrent infections or high-grade VUR [8, 9]. Studies have shown that abnormal DMSA findings are often correlated with higher grades of VUR (grade III and above) and recurrent febrile UTIs [10]. While abnormal DMSA scans are associated with a greater risk of renal damage and long-term complications, the presence of normal scans may reduce the necessity for more invasive procedures such as voiding cystourethrography (VCUG), especially after the first UTIs [10, 11]. Despite its diagnostic value, the prevalence and determinants of abnormal DMSA findings in CAKUT patients with VUR remain under investigation [12]. Understanding these factors is essential for optimizing management strategies and preventing long-term renal damage.

This study aimed to investigate the factors associated with abnormal DMSA findings in children diagnosed with VUR, with a focus on demographic variables, VUR severity, and presence of UTIs.

Material and Methods

This retrospective study was conducted on children with VUR who were followed at the Pediatric Nephrology Clinic of the Samsun Training and Research Hospital between January 2010 and December 2017. The study adhered to the ethical regulations and principles specified in the Declaration of Helsinki and received approval from the Ethical Committee of Samsun Training and Research Hospital (Date: 17.10.2017, Decision No. 155). The requirement for obtaining informed consent was waived by the Ethics Committee due to the retrospective design of the study.

Study Population and Data Collection

A total of 520 children diagnosed with CAKUT were retrospectively evaluated to assess their eligibility for the study. Patients with other CAKUT diagnoses, such as hydronephrosis (n = 332), renal agenesis (n = 32), multicystic dysplastic kidney (n = 15), ureteropelvic junction obstruction (n = 18), ectopic kidney (n = 15), posterior urethral valve (n = 1), horseshoe kidney (n = 20), hypoplastic kidney (n = 18), duplex collecting system (n =

24), ectopic ureter (n = 1), ureterocele (n = 1), bifid pelvis (n = 2), patients lost to follow-up (n = 1), or patients with incomplete or inaccessible records (n = 1) were excluded from the study. A total of 39 patients with a VUR diagnosis were included in the analyses.

Patient data were collected using the hospital's electronic information system and patient files. These data included demographic information such as gender, and age at diagnosis, duration of follow-up; clinical parameters such as diagnoses, serum creatinine, ultrasound findings; follow-up data such as UTIs, the use of VCUG and kidney scintigraphy (99mTc-DMSA).

Statistical Analysis

All data were analyzed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). Numerical data determined to be normally distributed based on the results of the Kolmogorov-Smirnov test are presented as mean ± standard deviation (SD) values. In contrast, non-normally distributed variables are presented as median (min-max) values. For comparisons between groups, Student's t-test and Mann-Whitney U test were used according to the normality of the distribution. Categorical variables were presented as numbers and percentages, and for inter-group comparisons, Fisher's exact test was used when the expected cell frequencies were less than 5, while the Chi-square test was used in other cases. Significance was accepted at $P < 0.05$ for all statistical analyses.

Results

The age at diagnosis ranged from 2 to 192 months, with the majority of patients being female (82.0%). All patients had abnormal prenatal and postnatal ultrasound findings. The degree of VUR was mostly Grade III (46.2%), and the frequency of bilateral VUR was 35.9%. The median follow-up time for the patients was 15 months, with a range of 3 to 84 months. UTIs were detected in 53.8% (n = 21) of the patients. UTIs were found in 16 girls (50.0%) and 5 boys (71.4%), and this difference between genders was statistically significant (p = 0.001). VCUG results were abnormal in all cases, and 69.2% had abnormal findings on the DMSA scan. The demographic and clinical characteristics of the patients are shown in Table 1.

The distribution of gender and age was comparable between patients with abnormal and normal DMSA scan results. While the ratio of VUR grade III and above was higher in the group with abnormal DMSA findings (81.5% vs. 50.0%, p = 0.046), there was no significant difference in the frequency of bilateral VUR between the groups (33.3% vs. 41.7%, p = 0.618). The frequency of UTIs appeared higher in patients with abnormal DMSA findings, but this difference did not reach statistical significance (63.0% vs. 33.3%, p = 0.090) (Table 2).

Table 1. Demographic and clinical characteristics of patients with vesicoureteral refux.

Variables	All population n = 39
Sex, n (%)	
Girl	32 (82.0)
Boys	7 (18.0)
Age at diagnosis, months	30 (2-192)
Prenatal ultrasound findings, n (%)	
Normal	-
Abnormal	39 (100)
VUR grade, n (%)	
I	2 (5.1)
II	9 (23.1)
III	18 (46.2)
IV	8 (20.5)
V	2 (5.1)
Bilateral VUR, n (%)	14 (35.9)
UTIs, n (%)	21 (53.8)
Age of diagnosis, months	7 (2-13)
Postnatal ultrasound findings, n (%)	39 (100)
Normal	-
Abnormal	39 (100)
VCUG findings, n (%)	
Normal	-
Abnormal	39 (100)
DMSA findings, n (%)	
Normal	12 (30.8)
Abnormal	27 (69.2)

DMSA, Tc-99 m dimercaptosuccinic acid; VCUG, voiding cystourethrography; VUR, vesicoureteral refux; UTIs, urinary tract infections.

Table 2. Findings associated with abnormal DMSA.

Variables	Normal DMSA n = 12	Abnormal DMSA n = 27	P-value
Sex, n (%)			
Girl	9 (75.0)	23 (85.2)	0.449*
Boys	3 (25.0)	4 (14.8)	
Age at diagnosis, months	27 (2-168)	33 (2-192)	0.135†
VUR grade, n (%)			
I-II	6 (50.0)	5 (18.5)	0.046*
>III	6 (50.0)	22 (81.5)	
Bilateral VUR, n (%)	5 (41.7)	9 (33.3)	0.618§
UTIs, n (%)	4 (33.3)	17 (63.0)	0.090*

§ Chi-square test. * Fisher's exact test. † Mann-Whitney U test. DMSA, Tc-99 m dimercaptosuccinic acid; VUR, vesicoureteral refux; UTIs, urinary tract infections.

Discussion

This study assessed the occurrence of abnormal DMSA kidney scans and the related factors in children diagnosed with VUR.

The main results showed a significant association between abnormal DMSA scans and higher VUR grades, though bilateral VUR was not significantly correlated. There was a trend toward higher UTI frequency in cases with abnormal DMSA scans.

In a study on CAKUT cases, renal scarring was detected in 13.8% of patients [13]. In children with renal ectopia, a study using DMSA scintigraphy found renal scarring in 27.9% of cases [14]. In a study of children with primary VUR, DMSA scintigraphy was normal in 14% of cases and abnormal in 86% [15]. In our study, 69.2% of patients had abnormal DMSA scan results. Additionally, gender distribution did not show a significant impact on abnormal DMSA findings. However, the majority of the study consisted of girls patients, which is consistent with some studies that report a higher incidence of VUR in girls [10, 16]. Despite this, previous research has produced conflicting results regarding the relationship between gender and VUR. Some studies suggest that VUR is more frequent in boys, particularly in the first few months of life, while others report a predominance of girl patients, especially as children grow older [17-19]. This discrepancy may be attributed to differences in the timing of diagnosis, with boys being more prone to VUR in early infancy and girls exhibiting a higher incidence later, often linked to recurrent UTIs [20]. The comparable distribution of age across both groups further reinforces that renal damage, as detected by DMSA scans, can occur at any age, influenced more by clinical factors like UTI frequency and VUR grade [16].

The study found a significant relationship between higher grades of VUR and abnormal DMSA results. Specifically, patients with VUR grade III or above were much more likely to have abnormal DMSA findings, highlighting the association between severe VUR and renal scarring [12]. In a study involving children who were diagnosed late with VUR, 83.9% of them had abnormal results on a DMSA renal scan. The median age of these children was 7.6 years, and they all had VUR of grade III to IV, which represents the more severe forms of the condition, indicating that higher grades of reflux are associated with worse kidney damage [21]. In a previous study, it was also found that abnormal DMSA rates in grade II, III, and IV were quite similar (49.4–59%), whereas grade I showed a significantly lower rate of 26.3%, and Grade 5 deviated significantly higher, with an abnormal rate of 78.8% [12]. In the RIVUR trial, the occurrence of abnormal DMSA findings varied across different VUR grades. Specifically, the rates were 7.6% for grade I, 4.7% for grade II, 10% for grade III, and significantly higher at 35.2% for grade IV [22]. These results highlight the increasing likelihood of renal scarring as the severity of VUR increases, with a notable jump from the lower to higher grades.

On the other hand, the ratio of bilateral VUR was relatively lower in patients with abnormal DMSA scan findings. A previous study demonstrated that unilateral VUR is an independent factor for abnormal DMSA scan findings, with this effect being more prominent in cases of high-grade VUR [12]. The authors proposed that this situation could be attributed to a congenitally dysplastic kidney [12]. It has been indicated that unilaterality is not related to the occurrence of renal scarring [22]. While bilateral VUR can increase the overall burden on the kidneys, it appears that the grade of reflux is a more critical factor in determining the likelihood of renal scarring. Other studies also support this conclusion, noting that renal damage is more strongly associated with the severity of VUR rather than its laterality [23, 24].

Studies have suggested a connection between DMSA scintigraphy results and recurrent UTIs [25, 26]. Studies have also indicated that febrile urinary tract infections significantly contribute to the pathophysiology of renal scarring [27-29]. In patients with abnormal DMSA scan findings, the frequency of UTIs was nearly twice as high compared to those with normal DMSA results. However, this difference did not reach statistical significance. This suggests that while UTIs are closely linked to renal scarring and abnormal DMSA results, factors such as sample size or other variables may have influenced the lack of statistical significance in this study.

This study has several limitations that should be acknowledged. First, the sample size was relatively small, which may have reduced the statistical power to detect significant differences between groups, especially in the comparison of UTI frequency between patients with abnormal and normal DMSA findings. Larger studies are needed to confirm the trends observed here. Second, the study population was drawn from a specific clinical setting, which may limit the generalizability of the findings to broader populations. Another limitation is the retrospective nature of the study. A prospective study would allow for better control over confounding variables, such as UTI frequency and management, and provide more accurate data on the timing of infections and the progression of renal damage. Lastly, the timing of the DMSA scans was not standardized across all patients. The variability in when the scans were performed following VUR diagnosis or infection

could affect the detection of renal scarring. Addressing these limitations in further research would help clarify the associations observed in this study and enhance the accuracy of its conclusions.

Conclusion

This study demonstrated a significant association between higher VUR grades and abnormal DMSA findings, indicating an increased risk of renal scarring in more severe cases. While UTIs were more frequent in patients with abnormal DMSA results, the difference was not statistically significant. The lack of a significant link between DMSA abnormalities and bilateral VUR or UTIs suggests that VUR severity is a more critical predictor of kidney damage.

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Conflicts of Interest

The authors declare they have no conflicts of interest.

Ethics Approval

The study was performed in accordance with the Declaration of Helsinki, and was approved by the Ethical Committee of Samsun Training and Research Hospital (Date: 17.10.2017, Decision No. 155).

Informed Consent

The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

Availability of Data and Material

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

Authors' contribution

Concept – H.G.Ö. and Y.S., Design- H.G.Ö. and Y.S., Supervision - Y.S., Data collection and/or processing - H.G.Ö. and Y.S., Analysis and/or interpretation - H.G.Ö. and Y.S., Writing – H.G.Ö., Critical review- Y.S. All authors read and approved the final version of the manuscript.

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Research Article

The diagnostic value of systemic inflammation indices in pregnant women with acute appendicitis and their relationship with the duration of hospital stay

Gebe kadınlarda akut apandisitli hastalarda sistemik inflamasyon indekslerinin tanısal değeri ve hastanede kalış süresi ile korelasyonu

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ABSTRACT

Aim: Physiological and anatomical changes occurring during pregnancy can complicate the diagnosis of acute appendicitis (AA). This study aimed to evaluate the diagnostic performance of systemic inflammation indices in distinguishing AA in pregnant women and to assess their relationship with hospital stay duration.

Material and Methods: This retrospective study encompassed 32 pregnant patients who underwent appendectomy and 32 healthy pregnant (control group). Systemic inflammation indices were calculated based on neutrophil (N), platelet (P), and lymphocyte (L) levels as follows: The neutrophil-to-lymphocyte ratio (NLR) = N/L; the platelet-to-lymphocyte ratio (PLR) = P/L; systemic immune-inflammation index (SII) = (N×P)/L.

Results: The AA group had higher median levels of PLR (30.9 vs. 22.4, $p = 0.035$), NLR (6.1 vs. 3.5, $p < 0.001$), and SII (1370 vs. 807, $p < 0.001$) compared to the control group. Systemic inflammation indices showed a positive correlation with the Alvarado score and the length of hospital stay. SII values demonstrated superior diagnostic performance in predicting AA compared to NLR and PLR values. The threshold value for SII in predicting AA was identified as >1316, with a sensitivity of 85.8% and a specificity of 72.5%.

Conclusions: Systemic inflammation indices, particularly SII, demonstrate strong diagnostic value in distinguishing AA in pregnant women. SII demonstrated superior accuracy over NLR and PLR, correlating with both the Alvarado score and hospital stay, suggesting its utility as a diagnostic and prognostic marker.

Keywords: acute appendicitis, Alvarado score, pregnancy, systemic inflammation indices, systemic immune-inflammation index

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ÖZ

Amaç: Gebelik sırasında meydana gelen fizyolojik ve anatomik değişiklikler, akut apandisit (AA) tanısını zorlaştırabilir. Bu çalışmada gebe kadınlarda AA'yı ayırt etmede sistemik inflamasyon indekslerinin tanısal performansının değerlendirilmesi ve hastanede kalış süresi ile ilişkisinin değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: Bu retrospektif çalışma, apendektomi uygulanan 32 gebe hasta ile 32 sağlıklı gebe (kontrol grubu) üzerinde gerçekleştirilmiştir. Sistemik inflamasyon indeksleri, nötrofil (N), trombosit (P) ve lenfosit (L) düzeylerine göre şu şekilde hesaplanmıştır: nötrofil-lenfosit oranı (NLR) = N/L; trombosit-lenfosit oranı (PLR) = P/L; sistemik immün-inflamasyon indeksi (SII) = (N×P)/L.

Bulgular: AA grubunda kontrol grubuna kıyasla PLR (30.9 vs. 22.4, p = 0.035), NLR (6.1 vs. 3.5, p < 0.001) ve SII (1370 vs. 807, p < 0.001) değerleri daha yüksek bulunmuştur. Sistemik inflamasyon indeksleri, Alvarado skoru ve hastanede kalış süresi ile pozitif korelasyon göstermiştir. SII, NLR ve PLR'ye göre AA'yı öngörmede daha yüksek tanısal performans sergilemiştir. AA'yı öngörmede SII için eşik değer >1316 olup, duyarlılık %85.8 ve özgüllük %72.5 olarak belirlenmiştir.

Sonuç: Sistemik inflamasyon indeksleri, özellikle SII, gebelerde AA'yı ayırt etmede güçlü tanısal bir değere sahiptir. SII'nin hem Alvarado skoru hem de hastanede kalış süresi ile korelasyon göstererek NLR ve PLR'ye göre üstün doğruluk gösterdiği ve tanı ve prognoz belirteci olarak yararlı olduğunu düşündürmektedir.

Anahtar Kelimeler: akut apandisit, Alvarado skoru, gebelik, sistemik inflamasyon indeksleri, sistemik immün-inflamasyon indeksi.

Introduction

Acute appendicitis (AA), often the primary surgical emergency in patients admitting to the emergency department with abdominal pain, also serves as the leading reason for non-obstetric surgeries during pregnancy. The reported incidence stands at 1 in 500 to 2000 pregnancies [1]. The diagnosis of AA becomes especially challenging during pregnancy due to the common occurrence of abdominal discomfort and gastrointestinal issues, alongside anatomical shifts owing to the enlarged uterus, and the typical leukocytosis seen in this period [2]. During pregnancy, the immediate diagnosis and treatment of AA are critically important due to its potential life-threatening complications for both the maternal and the fetus [3].

The diagnosis of AA necessitates integrating clinical assessments, laboratory findings, and radiological evaluations [4]. Recently, several studies involving pregnant women have demonstrated that inflammatory markers exhibit significant diagnostic capabilities in distinguishing patients with AA [5-7]. On the other hand, in pregnancy, physiological leukocytosis frequently occurs and is particularly linked with elevated neutrophil counts during the third trimester [8]. It has also been reported that in healthy pregnant women, there is an increase in inflammatory markers such as leukocytes and C-reactive protein (CRP) [3, 9]. This could also affect the diagnostic performance of inflammatory markers in pregnant women with AA. Additionally, conflicting results have been reported regarding the diagnostic role of comprehensive systemic inflammation indices in distinguishing these patients [5, 10-17].

We hypothesized that in pregnant women with AA, comprehensive new inflammation indices derived from different leukocyte parameters, such as the systemic immune-inflammation index (SII), as well as the neutrophil-to-lymphocyte ratio and the platelet-to-lymphocyte ratio, could be higher compared to healthy pregnant women. Therefore, this study aimed to investigate the diagnostic performance of systemic inflammation indices in distinguishing pregnant women with AA, as well as their correlation with the duration of hospital stay.

Material and Methods

This retrospective study was conducted on pregnant women between June 2018 and December 2023 in the Kutahya Health Sciences University General Surgery Clinic. All processes adhered to ethical guidelines and the principles outlined in the Declaration of Helsinki, as revised in Brazil in 2013. The study protocol received approval from the Kutahya Health Sciences University Faculty of Medicine Ethics Committee (Date: 05.03.2024 - No: 2024/03-21). Due to the retrospective design of the study, the local ethics committee waived the necessity for informed consent.

Previous studies have reported that the neutrophil-lymphocyte ratio (NLR) level in pregnant women with AA is approximately twice as high compared to healthy pregnant women (range of NLR for pregnant women with AA: 6.0-12.0; range of NLR for healthy pregnant women: 3.5-4.0) [10-15]. Accordingly, considering the mean NLR level to be 7.6±6.0 in pregnant women with AA and 3.8±3.0 in healthy pregnant women, it was determined that at least 31 patients are required for each group with a 5% margin of error and 90% power.

Study population

During the study period, a total of 176 pregnant women who were admitted to the emergency department due to abdominal pain were retrospectively evaluated. Patients with diabetes mellitus, hypertension, myocardial disorders, cancer or autoimmune diseases, hematological disorders, liver disease, kidney disease, chronic pulmonary diseases, infectious diseases, tobacco or alcohol use, prior antibiotic use, and those who underwent laparoscopic appendectomy, as well as those with incomplete records, were excluded from the study. After applying the exclusion criteria, the study included 32 pregnant women who were diagnosed with AA and received surgery, along with 32 patients identified as not having AA and who were not subjected to surgical intervention (control group). The control group was matched by age and gestational age to ensure comparability, enhancing the reliability of the study results.

Study protocol

Cases with suspected AA based on clinical findings underwent evaluation by ultrasound or magnetic resonance imaging (MRI) [18]. In cases of AA diagnosis, the appendectomy procedure was carried out using an open approach via a McBurney incision. Histopathological examinations confirmed the AA diagnosis. Patient electronic records were utilized to gather demographic and clinical information, including age, body mass index (BMI), gravida, parity, week of gestation, examinations findings, blood samples, and the duration of hospital stay.

The indices for inflammation were determined in the following manner: The platelet-to-lymphocyte ratio (PLR) = platelet count / lymphocyte count ratio; the NLR = neutrophil count / lymphocyte count; and SII = (platelet count × neutrophil count) / lymphocyte count [19, 20].

Statistical analysis

All analyses were conducted using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA) and Medcalc 11.4.2 (MedCalc Software, Mariakerke, Belgium) software. Categorical data were represented in terms of frequency and percentage. Group-wise comparisons were made utilizing the Chi-square test (with post-hoc cell-wise analysis) and the Fisher's Exact test. The normal distribution of numerical variables was assessed using the Kolmogorov-Smirnov test. Data exhibiting a normal distribution were presented as mean ± standard deviation, and comparisons between groups were made using the Student's T-test. Non-normally distributed data were displayed as median (interquartile range (IQR): 25-75 percentiles) and comparisons between groups were conducted using the Mann-Whitney U test. Stepwise multivariable logistic regression analysis was used to evaluate independent predictors of the AA. The evaluation of diagnostic performance was conducted through ROC analysis, and the cut-off values were determined using the Youden index method. Value of $p < 0.05$ were considered statistically significant.

Results

The study included 32 pregnant women with AA (mean age 27.2 ± 6.2 years) and a control group (mean age 26.9 ± 5.3 years). There were no significant demographic differences between the two groups. The mean leukocyte level (14.0 ± 4.7 vs. 10.0 ± 2.0 $x10^3$/µL; $p < 0.001$) and mean neutrophil level (11.3 ± 4.5 vs. 6.5 ± 1.4 $x10^3$/µL, $p < 0.001$) were higher in the AA group, while the median lymphocyte level was lower (1.4 vs. 1.8 $x10^3$/µL; $p < 0.001$). The AA group had higher median levels of PLR (30.9 vs. 22.4, $p = 0.035$), NLR (6.1 vs. 3.5, $p < 0.001$), and SII (1370 vs. 807, $p < 0.001$) compared to the control group (Table 1).

There was a positive correlation between the Alvarado score and PLR ($r = 0.291$, $p = 0.042$), NLR ($r = 0.326$, $p = 0.009$), and SII ($r = 0.397$, $p < 0.001$). Similarly, a positive correlation was observed between the length of hospital stay and PLR ($r = 0.295$, $p = 0.040$), NLR ($r = 0.315$, $p = 0.012$), and SII ($r = 0.374$, $p < 0.001$) (Table 2).

ROC Curve analysis, the SII demonstrated 85.8% sensitivity and 72.5% specificity for acute appendicitis diagnosis when a threshold of > 1316 was applied. SII values demonstrated superior diagnostic performance in predicting AA compared to NLR and PLR values (Table 3).

Table 1. Demographic and clinical findings

Variables	Acute Appendicitis n = 32	Control group n = 32	P-value
Age, years	27.2 ± 6.2	26.9 ± 5.3	0.658
Gravida	2 (1-3)	2 (1-3)	0.413
Parity	1 (0-2)	1.0 (0 -1)	0.322
Abortion	0	0	-
Trimester (%)			
First	14 (43.8)	15 (46.9)	0.864
Second	15 (46.9)	13 (40.6)	
Third	3 (9.4)	4 (12.5)	
Alvarado score	7 (6-9)	-	-
Laboratory findings			
Leukocytes, x103/µL	14.0 ± 4.7	10.0 ± 2.0	<0.001*
Lymphocytes, x103/µL	1.4 (1.3-2.3)	1.8 (1.6-2.1)	<0.001*
Neutrophils, x103/µL	11.3 ± 4.5	6.5 ± 1.4	<0.001*
Platelets, x103/µL	247.0 ± 56.6	233.4 ± 64.4	0.307
PLR	30.9 (20.7-40.1)	22.4 (17.6-35.0)	0.035*
NLR	6.1 (3.5-9.9)	3.5 (3.0-4.2)	<0.001*
SII	1370 (852-2251)	807 (639-953)	<0.001*
Hospital stay, day	3 (2-4)	-	-

Data are shown as mean ± SD or median (IQR) or number and percentage (%). *p<0.05 indicates statistical significance. Abbreviations: NLR, neutrophil to lymphocyte ratio; PLR, platelets to lymphocyte ratio; SII, systemic immune inflammation index.

Table 2. Parameters associated with Alvarado score and hospital stay.

Variables	Alvarado score		Hospital stay	
	r	p	r	p
Age	0.092	0.617	0.009	0.959
Trimester	-0.080	0.662	-0.001	0.996
Leukocytes	0.319	<0.001*	0.305	<0.001*
Lymphocytes	-0.314	<0.001*	-0.306	0.005*
Neutrophils	0.314	<0.001*	0.298	0.018*
Platelets	0.318	<0.001*	0.292	0.027*
PLR	0.321	<0.001*	0.305	<0.001*
NLR	0.336	<0.001*	0.315	<0.001*
SII	0.397	<0.001*	0.374	<0.001*
Hospital stay	0,337	<0,001*	-	-

*p<0.05 indicates statistical significance. Abbreviations: NLR, neutrophil to lymphocyte ratio; PLR, platelets to lymphocyte ratio; SII, systemic immune inflammation index.

Table 3. ROC analysis was performed to assess the predictive accuracy of preoperative laboratory findings in diagnosing appendicitis.

Results	PLR	NLR	SII
AUC ± SE	0.60 ± 0.05	0.75 ± 0.08	0.81 ± 0.04
Threshold value	> 150.5	> 4.8	> 1316
Sensitivity, %	61.7	74.6	85.8
Specificity, %	59.2	70.2	72.5

Abbreviations: AUC, area under the curve, NLR, neutrophil to lymphocyte ratio; PLR, platelets to lymphocyte ratio; SE, standart error; SII, systemic immune inflammation index.

Discussion

This study investigates the diagnostic utility of systemic inflammation indices, specifically NLR, PLR, and SII, in pregnant women with AA. The findings confirm that these hematologic markers, especially SII, exhibit strong correlations with clinical outcomes, such as hospital stay duration and disease severity. The results not only support their diagnostic value but also suggest that they may serve as valuable, accessible tools in settings where traditional imaging methods are either unavailable or present risks to the fetus [21]. Given the limitations of radiological diagnostics in pregnancy, these biomarkers offer an alternative or supplementary approach to enhance the diagnostic accuracy of AA, a condition where delayed treatment can have serious maternal and fetal consequences.

Various scoring systems have been developed to support the early diagnosis of acute appendicitis, typically relying on physical examination, laboratory results, and imaging. While these methods are simple and cost-effective, there is no scoring system specifically designed for pregnant women. Most studies focus on non-pregnant patients, with the Alvarado score being the most widely used. In pregnancy, its sensitivity and specificity have been reported to range between 69-86% and 61-77%, respectively [22, 23]. Pregnancy-related symptoms like nausea and abdominal pain can complicate diagnosis, requiring additional imaging, such as ultrasonography and MRI. Ultrasound is favoured for its accessibility and safety but is less reliable in later pregnancy stages [24, 25]. Weight gain related to pregnancy, differences in the anatomical location of the appendix, air in the intestinal loops, and operator experience affect the diagnostic accuracy of ultrasonography [26]. MRI, though more expensive and less accessible, offers higher diagnostic accuracy, with studies showing sensitivity and specificity rates of 91.8% and 97.9% [27]. Therefore, there is a need for easily accessible and inexpensive indicators that can predict AA in pregnant women.

Studies have examined the use of inflammatory markers in diagnosing inflammatory conditions in pregnant women with AA [5, 10-17]. In our study, NLR and PLR were significantly elevated in the AA group compared to controls, reflecting the heightened systemic inflammatory response associated with AA. These findings are consistent with the study of Çınar et al. and Güler et al., who both reported similar elevations in these markers among pregnant AA patients [10, 14]. The pathophysiological mechanism underlying this is likely due to the sharp increase in neutrophils in response to infection and tissue damage, alongside a relative decrease in lymphocyte counts, which contributes to the rise in these ratios. Importantly, the diagnostic utility of NLR and PLR in pregnant women is critical because these indices can help distinguish between normal pregnancy-related changes, such as physiological leukocytosis, and more severe inflammatory states like AA [21]. Yazar et al. conducted a retrospective analysis of 78 pregnant women suspected of having AA [11]. The study found that those with pathologically confirmed appendicitis exhibited significantly higher levels of CRP, white blood cell count, NLR, and PLR compared to both pregnant women without appendicitis and healthy control groups, including non-pregnant individuals. These markers were notably elevated in the appendicitis group, highlighting their potential diagnostic utility in distinguishing between healthy pregnancies and those complicated by appendicitis. The authors reported that the combination of WBC count, NLR, PLR, CRP levels, and lymphocyte count demonstrated 90% accuracy in predicting the diagnosis of AA [11].

The findings related to SII in this study are particularly noteworthy. SII, which integrates neutrophil, platelet, and lymphocyte counts into a single marker, was found to be superior to both NLR and PLR in predicting AA, with an AUC of 85.8% at a threshold of 1316. This result is in line with recent literature emphasizing SII's ability to provide a more comprehensive measure of the systemic inflammatory response. Telaferli et al. have demonstrated the utility of SII in complex inflammatory and infectious conditions, where it often surpasses traditional markers in sensitivity and specificity [17]. A study led by Güler et al. reported that SII levels demonstrated a lower accuracy rate in predicting acute appendicitis in pregnant women, compared to leukocyte and neutrophil levels [14]. The difference between the studies may be due to the inclusion criteria of the patients. The significantly higher SII levels observed in our AA group suggest that this index could serve as a powerful tool for early identification of AA in pregnant women, a population where timely diagnosis is often hampered by overlapping clinical symptoms with pregnancy, such as nausea, vomiting, and abdominal discomfort. Also, SII combines neutrophil, platelet, and lymphocyte counts into a single marker, providing a more comprehensive reflection of the systemic inflammatory response. This integration may explain its superior diagnostic and prognostic performance compared to NLR and PLR, which assess fewer components of the inflammatory response.

A another finding of our study is the positive correlation between SII and the Alvarado score, which underscores the potential benefit of combining systemic inflammatory indices with established clinical scoring systems. The Alvarado score is widely used in diagnosing AA, but its application in pregnancy has been less validated, as pregnancy-related physiological changes can obscure some of its clinical components, such as rebound tenderness or leukocytosis [28, 29]. By integrating SII

into the diagnostic process, clinicians may be able to refine the Alvarado score's predictive power, particularly in ambiguous cases where imaging is not conclusive. Furthermore, the significant correlation between SII and hospital stay duration reinforces the utility of this marker not only as a diagnostic tool but also as a prognostic indicator. Patients with higher SII values may be more prone to prolonged recovery times, which could guide decisions regarding postoperative monitoring and care. Studies suggest that higher SII values are associated with more severe cases of appendicitis, including complicated cases, and these values can help differentiate between uncomplicated and complicated appendicitis in pregnant patients [30]. In cases where appendicitis is complicated, pregnant women tend to have longer hospital stays, driven by the need for more intensive management, including possible surgical interventions like appendectomy [1, 30].

This study has several limitations. First, the relatively small sample size may limit the generalizability of the results. Larger, multicentre studies would be required to confirm the diagnostic thresholds and improve the robustness of the findings. Second, while systemic inflammation indices such as NLR, PLR, and SII are useful markers of inflammation, they are not specific to AA. These indices can also be elevated in other inflammatory conditions, such as urinary tract infections or cholecystitis, which are common in pregnancy [31]. Additionally, the retrospective nature of the study introduces potential biases, particularly in the collection and interpretation of clinical data. Moreover, the study did not account for the distinction between complicated and uncomplicated appendicitis, which may influence both clinical management and outcomes. Future prospective studies could help to minimize these biases and better control for confounding factors.

Conclusion

This study demonstrates that systemic inflammation indices, particularly SII, offer strong diagnostic value for acute appendicitis in pregnant women. The significant correlations between SII and both the Alvarado score and hospital stay duration highlight its potential as both a diagnostic and prognostic tool. In the context of pregnancy, where traditional imaging methods may pose risks or be less effective, incorporating systemic inflammation markers into clinical practice could improve the early detection and management of AA, ultimately leading to better maternal and fetal outcomes. Further research, particularly large-scale prospective studies, is needed to validate these findings and establish standardized diagnostic protocols for the use of systemic inflammation indices in pregnancy.

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Conflicts of Interest

The authors declare they have no conflicts of interest.

Ethics Approval

The study was approved by the Kutahya Health Sciences University Faculty of Medicine Ethics Committee (Date: 05.03.2024 - No: 2024/03-21).

Availability of Data and Material

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

Authors' contribution

Concept – B.I.C., Design- B.I.C. and M.A.T.; Supervision - BIC; Data collection and/or processing – B.I.C. and M.A.T., Analysis and/or interpretation - B.I.C. and M.A.T. Writing – BIC; Critical review- MAT. All authors read and approved the final version of the manuscript.

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Review

An Overview of Abdominoplasty

Abdominoplasti: Güncel Konseptler

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Abstract

The number of tummy tuck surgeries has recently increased significantly, largely due to the rise in bariatric surgery procedures. This surgical procedure is undertaken for both functional and aesthetic reasons. Several surgical techniques may be employed in the performance of an abdominoplasty. Most techniques are based on the excision of the skin in the lower abdomen and the stretching of the skin in the upper abdomen to cover the resulting defect. It is not feasible to utilize a singular technique for each patient. A meticulous assessment of the patient is imperative in determining the optimal technique. The advent of liposuction has provided a valuable adjunct to surgical intervention. This article outlines the evolution of abdominoplasty and the role of liposuction techniques in its development. Furthermore, the outcomes of the surgical method for reducing abdominal flap thickness by tangential excision of the abdominal flap before the advent of liposuction techniques are presented. Abdominal contouring procedures offer patients not only an enhancement in their appearance but also an improvement in their quality of life. Despite the numerous options, it is crucial to select a body contouring procedure that is safe and effective by evaluating the needs and expectations of each patient.

Keywords: Abdominoplasty, liposuction, bariatric surgery

Öz

Karın germe ameliyatları bariatrik cerrahi girişimlerinin artması nedeni ile son dönemde yeniden sık yapılan ameliyatlar arasına girmiştir. Bu cerrahi, estetik olduğu kadar fonksiyonel amaçlar güdülerek de yapılmaktadır. Abdominoplasti yapmak için kullanılan farklı cerrahi teknikler vardır. Çoğu teknik, karnın alt kısmındaki derinin eksizyonuna ve ortaya çıkan defekti örtmek için karnın üst kısmındaki derinin gerilmesine dayanır. Her hastaya tek tekniğin uygulanması mümkün değildir. Teknik seçiminde hastanın özenli değerlendirilmesi esastır. Liposuction tekniklerinin gelişimi cerrahi girişime çok büyük bir destek olmuştur. Bu yazıda abdominoplastinin bugüne kadar olan gelişimi, liposuction tekniklerinden bahsedilmiştir. Ayrıca, liposuction tekniklerinin gelişiminden önce abdominal flebin tanjansiyel eksizyonu ile abdominal flep kalınlığını azaltmaya yönelik cerrahi yaklaşımın sonuçları paylaşılmıştır. Karın şekillendirme prosedürleri hastalara sadece imajlarında bir düzelme sağlamaz aynı zamanda yaşam kalitelerinde bir iyileşmede sağlar. Birçok seçeneğe rağmen, her hastanın ihtiyacı ve talepleri değerlendirilerek hem güvenli hem de etkili bir vücut şekillendirme prosedürü seçmek esastır.

Anahtar Kelimeler: Abdominoplasti, liposuction, bariatrik cerrahi

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The abdominal Anatomy

The anterior abdominal wall is a complex structure of skin, subcutaneous adipose tissue, fascia, and muscles. In addition to surrounding the important organs, it is involved in functions such as standing, walking, bending, lifting, urination, defecation, labor, vomiting, coughing, and respiration [1]. The shape of the anterior abdominal wall may be impaired due to rapid weight loss, recurrent pregnancies, previous surgeries, hernias, obesity, and laxity of the anterior abdominal wall muscles [2]. Generally, cases showing deformities of the anterior abdominal wall can be classified into three groups according to their severity; mild (loose skin, few striae, mild fat accumulation, non-severe diastasis recti), moderate (toned, sagging skin, diastasis recti, striae, very prominent fat accumulation) and severe (very large amount of fat accumulation, enlargement and sagging of the abdominal skin, skin folds above the pubis or in the form of overflowing apron) [3].

The definition of Abdominoplasty

Abdominoplasties are functional and aesthetic surgeries aimed at correcting deformities of the skin, subcutaneous adipose tissue, muscles, and fascia. Over the past century, there have been many surgeons who have defined different abdominoplasty techniques to achieve better shaping and to hide the remaining scar [4]. Abdominoplasty techniques date back to 1870 [5]. Technical aspects of abdominoplasty have evolved significantly over the last two decades [6]. Many innovations were introduced by Lockwood, who emphasized the treatment of lateral lower abdominal skin laxity using a high lateral tension approach, lifting the flap in a specific area to preserve cutaneous perforating blood vessels, and a low scar position [7]. Preservation of the rectus abdominis muscle perforators increase the vascularity to the fat layer and skin of the abdominoplasty flap, allowing additional liposuction to be safely applied to this flap. In a full abdominoplasty, the length of the lower transverse incision extends laterally over a variable distance [8]. The span of the incision depends largely on the degree of skin folds or overhanging skin and the amount of vertical excess skin in the upper and lower abdomen. This usually extends beyond the anterior superior iliac process (ASIS) and may extend laterally to the posterior axillary line in extended abdominoplasty procedures [9]. Short scar procedures or 'mini' abdominoplasties are less common and can be performed when no excess skin in the upper abdomen and limited skin resection is needed in the lower abdomen. Excess adipose tissue can be removed tangentially from the abdominal flap to prevent umbilicus malposition, seen in abdominoplasty and affects the aesthetic appearance, and step-shaped skin residue caused by inappropriate flap thickness at the inguinal suture line.

The Brief History of Abdominoplasty

The first examples of abdominoplasty operations were on hernia and consisted of removing excess skin in large and sagging abdomens. Here, the excess skin was removed as a full layer without lifting the abdominal skin as a flap. Demars and Marx (1890) published cases of fat removal from the anterior abdominal wall in France. Kelly (1899) was the first physician to use the term 'abdominal lipectomy' in the history of medicine by publishing a study he conducted in the USA. Guadet and Morestin (1905) published a series of cases of transverse repair of large umbilical hernias and removal of excess skin and fat tissue. Desjardins (1911) used vertical elliptical excision and H. Morestin (1911) published his series of 5 cases with transverse incision, the largest series up to that time. Weindhold (1909) published a series of midline excisions in Germany. Jolly (1911) described the inferior transverse elliptical incision; Schepelman (1918) described vertical midline excisions. Thorek (1939) published the technique called plastic adipolipectomy. Thorek first took the navel as a graft and adapted it to its new location. Later, he left the navel in the abdominal wall and at the end of the operation, he removed and sutured it in a new place prepared in a flap on the anterior abdominal wall. Somalo (1946) used the term 'abdominal dermolipectomy' for the first time, which is still accepted as terminology today [10].

The Today of Abdominoplasty

Today, the difference in the application of abdominoplasty is due to the type of cut chosen. Korre (1952) categorized the cuts used in abdominoplasty [5, 11]. According to this:

1-Vertical: It runs between the processus xiphoideus and pubis and is recommended in cases of horizontal abdominal skin excess and looseness of the anterior abdominal wall structures in the same direction. This type of cut was used by Babcock, Pick, Ksuter, Spira.

2-Transverse: Nowadays, inferiorly located ones are often preferred. This type of cut was used by Somalo, Spadofora, Pitanguy, Gonzalez-Ulluoa, Molbeck, Regnault.

3-Combined: These are a mixture of transverse and vertical cut shapes. Today, this technique is used in patients with excess vertical and transverse skin after bariatric surgery.

Today's abdominoplasty operations aim to remove excess skin and fat tissue, to correct the anterior abdominal wall

muscles and fasciae and laxity, and to leave the smallest and most acceptable scar possible [12]. Various studies have been carried out on methods suitable for these purposes.

There is a concern among plastic surgeons that fat excision from the inner face of a raised abdominal flap or liposuction of this flap will disrupt skin circulation and cause additional wound-related complications. This has led to permanent central fullness and excess fat. Surgical removal of adipose tissue has been performed by many surgeons before and has been recommended in many scientific meetings [13, 14].

A surgical technique to reduce abdominal flap thickness

Taner et al. evaluated the results of 15 abdominoplasty operations performed in the 2nd Plastic and Reconstructive Surgery Clinic of Ankara Numune Hospital between 1983 and 1989. In the cases included in the study, thick abdominal flaps were thinned by tangential removal of excess adipose tissue. In these cases, standard abdominoplasty incision and flap elevation were performed. After excision of the part under the umbilicus, the adipose tissue under the superficial fascia was removed tangentially from the remaining abdominal flap with a dermatome knife. Following hemostasis, the umbilicus was adapted to its new location and the subcutaneous skin was sutured in three layers after drain placement. In the patients included in the study, tangential adipose tissue was removed from the right half of the abdominal flap in combination with classical abdominoplasty, and no surgical procedure was performed on the left half to reduce the thickness of the abdominal flap in the first session. Postoperative necrosis, irregularity, ecchymosis, hyperpigmentation, edema, thrombophlebitis, pulmonary embolism, umbilical malposition, asymmetry, and excess residual adipose tissue were not observed. In our case in which tangential excision was performed on the right half, umbilical malposition, asymmetry on the anterior abdominal wall, and a prominent left-sided step deformity on the inguinal incision line were observed (17). While similar studies have continued until today, their results have been reported in various publications. For example, Samra et al (2010) studied on the authors conducted a chart review of 161 patients who had undergone either lipoabdominoplasty or traditional abdominoplasty between 2004 and 2009. They reported that Lipoabdominoplasty was not associated with a statistically significant increase in perfusion-related complication rates compared with classical abdominoplasty, even though it involves potential trauma to the vascularity of the elevated abdominoplasty flap. This holds even in patients who are at increased risk for perfusion-related complications secondary to a history of active smoking or a previous supraumbilical scar [15].

Vieira et al (2018) studied in Eleven thousand one hundred ninety-one patients having abdominoplasty with truncal liposuction and having abdominoplasty alone. Overall complication rates were 10.5 percent and 13.0 percent, respectively. Combined liposuction and abdominoplasty were independently associated with a reduced risk of overall complications and seroma. They reported that abdominoplasty with truncal liposuction is safe, with fewer complications than abdominoplasty alone [16].

Discussion and Future Direction

Patients who apply for abdominoplasty are usually middle-aged and elderly people, who have given birth to many children, whose skin quality has deteriorated, whose abdominal skin is sagging, often overhanging the pubis, who have excessive fat accumulation in the abdominal region, and who are obese or tend to obesity. In these patients, deformities of the superficial fat layer are common [17].

If the thick abdominal skin flap is not thinned in tummy tuck surgeries, the potential for obesity will remain hidden due to the deep fat layer that will remain especially below the navel for the person's future life. These cells may hypertrophy by storing fat again. If calorie intake continues, new fat cells will be formed in this layer from cells called adipocytes. These cells are resistant to both diet and exercise.

The weight gained in this way cannot be lost later. The total fat storage capacity of the remaining cells will decrease due to the number of cells removed by previous surgery. If the person does not abandon the preoperative eating habits, it will be easier for the response to be hyperplasia at the cellular level than in the preoperative period. Again, in case of weight gain, since the symmetry of the deep fat layer, which is normally symmetrically distributed around the navel in the preoperative period, will be disrupted after surgery, fat storage will show an asymmetrical distribution in case of obesity. The accumulation of features will be below the new belly.

In cases where the abdominal flap is not thinned, the possibility of step deformity because of inappropriate flap thickness on the inguinal suture line is very high. Many different procedures are performed to thin the thick flap. Surgical removal of adipose tissue, previously performed by many surgeons, is still used today. This technique was proposed by Pontes, Riberio, Busker, Galli and Reqnualt, but no specific study is available

[17]. As shown in the study of Taner et al., tangential removal of adipose tissue technically did not cause problems such as necrosis and irregularity in the abdominal flap [18].

Nowadays, liposuction is frequently used for thinning of abdominal flaps. Illouz described a 'suction abdominoplasty' technique in 1992. This technique has been useful for those with abundant loose fat in the supraumbilical region [19].

Liposuction combined with abdominoplasty has proven safe and effective, but how much fat can be safely removed without increasing complication rates? An article published in 2009 summarized the lipoabdominoplasty procedure and the low complication rates seen with this technique [15]. Many authors have published their own experiences demonstrating safe and superior results using lipoabdominoplasty compared to abdominoplasty or liposuction alone. These publications show that liposuction performed simultaneously with abdominoplasty has the same or less morbidity than abdominoplasty alone when performed in safe areas [20-23].

Despite all this, the combination of liposuction with abdominoplasty, termed lipoabdominoplasty, remains a controversial topic due to reports of thrombotic or fat embolism complications and the possibility of liposuction-induced necrosis of the vascular supply of the abdominal wall flap. Using Huger's description of the three vascular territories of the abdominal wall, an attempt has been made to define what changes in technique are necessary to make lipoabdominoplasty a safe and effective procedure [15, 24].

Matarasso identified four areas that can be safely treated with liposuction when performing abdominoplasty, recommended limited and careful liposuction when combined with abdominoplasty, and stated that patients with vertical scars, large abdominal flap lifts, and smokers have the highest risk of flap necrosis in the combined procedure [25]. Heller et al. described liposuction of the entire abdomen, including the epigastric and mesogastric regions, followed by abdominoplasty and reported that complication rates did not increase in patients undergoing the combined procedure [26].

The development of vacuum-assisted liposuction (SAL)/ ultrasound-assisted liposuction (UAL) has changed the approach to body contouring surgery. Almost all plastic surgeons use SAL/UAL as an adjunct to excisional abdominoplasty [27, 28]. There are also liposuction techniques called VASER, which are combined with abdominoplasty and provide muscle definition. The surgical use of ultrasound or LASER is emphasized to enhance skin tightening during liposuction and enable the creation of varying degrees of muscle-like appearance [27]. These 'super-thin' flaps are possible using a specially designed liposuction cannula. In this way, the surgeon can proceed in a highly superficial manner, removing fat and preserving the subdermal plexus [27]. Both technologies facilitate fat removal and potentially reduce bleeding and cause less swelling and bruising. On the other hand, there is a higher incidence of thermal injury, dyschromia and seroma compared with normal SAL, as well as a longer procedure time [29].

Good results can be obtained with conventional lipoabdominoplasty, but liposuction results in a fatty thick abdominal flap compared to abdominoplasty. Thinner flaps with good blood supply can be obtained with liposuction, if they are applied to safe areas. Tangential fat excision from the abdominal flap presented by Taner et al. has been replaced by liposuction applications today. In these device-dependent applications, access to the device may not always be possible. It should be kept in mind that tangential fat excision can be performed safely in cases where a thick abdominal flap is encountered, and liposuction devices cannot be accessed or in the face of a situation that may cause a spike effect on the suture line.

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Case Report

Ultrasonic-assisted wound debridement: An emerging treatment modality for recalcitrant diabetic foot ulcers

Ultrasonik cerrahi debridman sistemleri: İnatçı diyabetik ayak ülserleri için güncel bir tedavi yöntemi

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Abstract

Chronic wounds remain one of the most challenging problems facing healthcare professionals with their ever-increasing impact on various domains of healthcare and well-being . Numerous management modalities have been proposed to reduce the clinical burden and healthcare costs associated with chronic wounds . Given the pivotal role debridement plays in wound care, it became a focus of interest for new therapeutic strategies in recent years . Herein, we report our experience with the Syllable™ Ultrasonic Surgical Debridement System manufactured by Mavera Medical Devices Inc. in a patient presenting with recalcitrant grade 3 stage D diabetic foot ulcers by the UT (University of Texas) system.

Keywords: ultrasonic debridement, bioburden, diabetic foot ulcer, biofilm

Öz

Kronik yaralar, giderek artmakta olan etkileriyle sağlık profesyonellerinin karşılaştığı en zorlu sorunlardan biri olmaya devam etmektedir. Kronik yaralarla ilişkili klinik yükü ve sağlık maliyetlerini azaltmak için birçok modalite önerilmiştir. Debridman, yara bakımında oynadığı kritik rol nedeniyle son yıllarda yeni terapötik stratejiler için ilgi odağı haline gelmiştir. Bu vaka raporunda, geleneksel tedaviye dirençli, UT sistemine göre grade 3 stage D diyabetik ayak ülseri ile başvuran bir hasta üzerinde kullanılan Syllable™ Ultrasonik Cerrahi Debridman Sistemi ile olan deneyimimizi sunuyoruz.

Anahtar Kelimeler: ultrasonik debridman, biyoyük, diyabetik ayak ülseri, biyofilm

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Introduction

Diabetic foot ulcers (DFUs) represent the leading cause of non-traumatic lower extremity amputations and hospital admissions in diabetic patients. The triad of neuropathy, peripheral arterial disease, and secondary infection has been shown to be the underlying mechanism for the development of DFUs. The success of limb salvage and definitive reconstruction depends on addressing each of these components with pressure off-loading, glycemic control, treatment of comorbidities, revascularization measures and above all, local wound care. Elimination of devitalized tissue, preservation of viable tissue and inhibition and eradication of the biofilm are all matters of paramount importance in wound bed preparation. There is an emerging interest in ultrasound-assisted wound debridement which offers, unlike mechanical and surgical debridement, a selective debridement option with effective removal of the biofilm, minimal patient discomfort, and shorter downtime. Multiple studies in recent years have yielded evidence that UAW (Ultrasonic-Assisted Wound Debridement) can be a rational alternative to surgical wound debridement. Our experience with the Syllable™ UAW system is consistent with the literature in terms of non-inferiority and in some respects, superiority.

Case

A 52-year-old patient with a medical history of uncontrolled, long-standing diabetes mellitus type 2, coronary artery disease, carotid stenosis and peripheral artery disease (PAD) presented to the wound care center with a rapidly evolving ulcer on the plantar surface of the left foot and wet gangrene of the 4th digit. Physical examination revealed a plantar ulcer involving deeper structures and wet gangrene of the 4th and 5th digits (figure 1). Absent pedal pulses and chronic PAD-related changes were noted bilaterally. Metatarsal periosteal reaction and cortical irregularities were noted in the radiographs pointing in the direction of metatarsal osteomyelitis. Initial lab workup showed elevated acute phase reactants (APRs) with a WBC of 24 × 109/L and a CRP of 242 mg/L, compatible with diabetic foot infection. The patient was admitted to our wound care center, wound cultures were obtained and the patient was put on broad-spectrum antibiotics. Wound culture results revealed a growth of Proteus mirabilis and multidrug-resistant Acinetobacter baumannii. A lower extremity computed tomography angiography (CTA) was obtained which revealed a left-sided total occlusion of the posterior tibial artery (PTA) and the fibular artery and critical stenosis of the anterior tibial artery (ATA) and the tibial-fibular trunk. The cardiology department was consulted to achieve revascularization of the limb. ATA was successfully revascularized with percutaneous balloon angioplasty while PTA remained occluded. Immediately after the revascularization, metatarsophalangeal disarticulation was performed for the necrotic digits and a more conservative approach was adopted for the plantar defect. Weekly sharp wound debridement was performed with no signs of improvement (figure 2). Following the failure of surgical debridement and the persistence of subacute osteomyelitis, the Syllable™ Ultrasonic Surgical Debridement System was used on the wound bed on a twice-a-week basis. After 6 sessions of UAW debridement combined with NPWT, a well-granulated wound bed was achieved with negative culture results. Following the initiation of UAW, APRs showed a steady decrease and by the 3rd week, CRP and WBC were in the normal range.

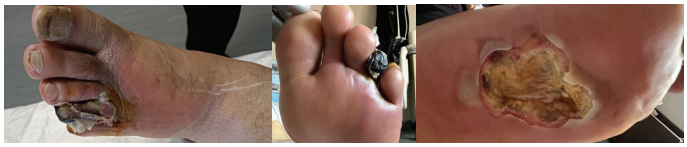

Figure 1. initial presentation

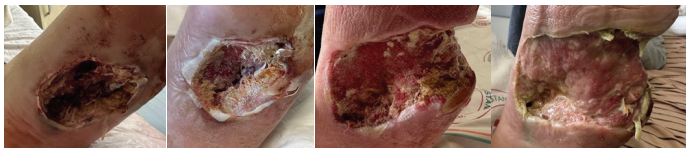

Figure 2. timeline of wound progression prior to UAW, demonstrating expansion of the wound and persistence of debris despite attempts at surgical debridement combined with NPWT.

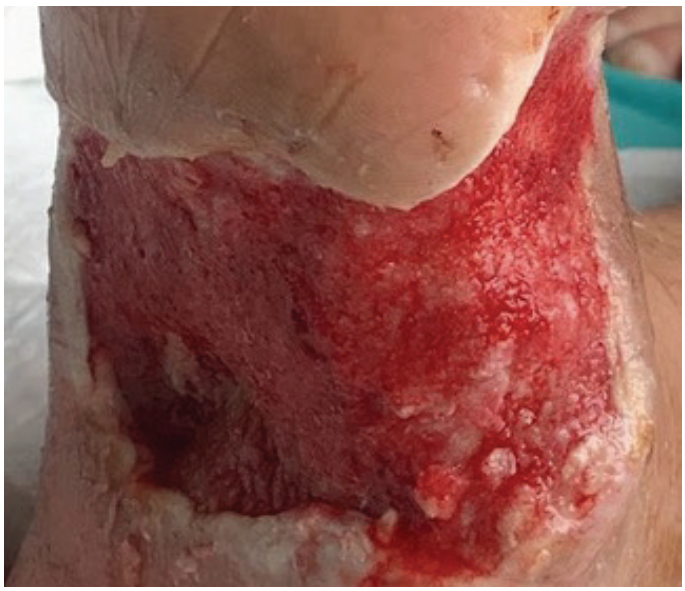

Figure 3. Wound bed following 6 sessions of UAW debridement, demonstrating healthy granulation tissue, prepared for definitive reconstruction.

Discussion

UAW debridement systems rely on ultrasonic activation of a liquid medium with low-frequency ultrasonic waves created by sonotrodes to generate microbubbles in the wound bed. Upon collapse of the microbubbles, ultrasonic energy is transformed into heat, disintegrating slough, necrosis and biofilm, effectively debriding the wound bed, reducing the bioburden, and preparing it for definitive reconstruction or healing by secondary intention. A myriad of other mechanisms, mostly of a chemical nature, have been suggested for the apparent effectivity of UAWs ranging from depolymerization of molecules to augmentation of oxidative processes, but the physical process of cavitation is believed to be the main mechanism underlying its well-founded success in wound bed preparation. In addition to UAWs's ability to selectively debride the wound bed, UAWs allow efficacious removal of the biofilm for which available and effective treatments are scarce. The Syllable™ Ultrasonic Surgical Debridement System by Mavera Medical Devices Inc. (Ankara, Türkiye) was used on our patient on multiple occasions in both inpatient and outpatient settings, NPWT was used in between each session as an adjunct to UAW debridement.

Conclusion

Diabetes remains the leading cause of lower extremity amputations. With its incidence projected to double by 2030 compared to the figures from 2000 , local wound care and other limb salvage interventions have become increasingly crucial in the management of DFUs. Meticulous wound bed preparation and minimizing bioburden lie at the root of wound care, failure of which often mandates amputations. With the recent increase in studies yielding evidence for UAWs' ability to eradicate/suppress biofilm and prepare the wound bed, UAWs have become a subject of interest for wound care specialists. As the psychological, social, and economic burden of diabetic foot ulcers continues to increase, the need to enhance patient comfort while ensuring adequate debridement becomes vital. Given the central role debridement plays in wound bed preparation and ultimately limb salvage, the demand for effective, efficient, and easy-to-operate debridement modalities grows. UAW systems excel among their competitors with claims of effective reduction of bioburden and preservation of vital tissue. This report intends to investigate whether UAW is up to par with surgical debridement. Our experience with the Syllable™ Ultrasonic Surgical Debridement System parallels the current literature. With its reliable performance and easy-to-use, intuitive design UAW systems offer a strong alternative to traditional surgical debridement in hard-to-heal wounds.

Conflict of Interest

The authors have no conflict of interest associated with this report.

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Etik kurallar: Klinik araştırmaların protokolü etik komitesi tarafından onaylanmış olmalıdır. İnsanlar üzerinde yapılan tüm çalışmalarda, "Yöntem ve Gereçler" bölümünde çalışmanın ilgili komite tarafından onaylandığı veya çalışmanın Helsinki İlkeler Deklerasyonuna (www.wma.net/e/policy/b3.htm) uyularak gerçekleştirildiğine dair bir cümle yer almalıdır. Çalışmaya dahil edilen tüm insanların bilgilendirilmiş onam formunu imzaladığı metin içinde belirtilmelidir. Turkish Journal of Clinics and Laboratory gönderilen yazıların Helsinki Deklarasyonuna uygun olarak yapıldığını, kurumsal etik ve yasal izinlerin alındığını varsayacak ve bu konuda sorumluluk kabul etmeyecektir.

Çalışmada "Hayvan" öğesi kullanılmış ise yazarlar, makalenin Gereç ve Yöntemler bölümünde Guide for the Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html) prensipleri doğrultusunda çalışmalarında hayvan haklarını koruduklarını ve kurumlarının etik kurullarından onay aldıklarını belirtmek zorundadır.

Teşekkür yazısı: Varsa kaynaklardan sonra yazılmalıdır.

Maddi destek ve çıkar ilişkisi: Makale sonunda varsa çalışmayı maddi olarak destekleyen kişi ve kuruluşlar ve varsa bu kuruluşların yazarlarla olan çıkar ilişkileri belirtilmelidir. (Olmaması durumu da "Çalışmayı maddi olarak destekleyen kişi/kuruluş yoktur ve yazarların herhangi bir çıkar dayalı ilişkisi yoktur" şeklinde yazılmalıdır.

Kaynaklar: Kaynaklar makalede geliş sırasına göre yazılmalıdır. Kaynaktaki yazar sayısı 6 veya daha az ise tüm yazarlar belirtilmeli, 7 veya daha fazla ise ilk 3 isim yazılıp ve ark. ("et al") eklenmelidir. Kaynak yazımı için kullanılan format Index Medicus'ta belirtilen şekilde olmalıdır (www.icmje.org). Kaynak listesinde yalnızca yayınlanmış ya da yayınlanması kabul edilmiş veya DOI numarası almış çalışmalar yer almalıdır. Dergi kısaltmaları "Cumulated Index Medicus" ta kullanılan stile uymalıdır. Kaynak sayısının araştırmalarda 25 ve derlemelerde 60, olgu sunumlarında 10, editöre mektupta 5 ile sınırlandırılmasına özen gösterilmelidir. Kaynaklar metinde cümle sonunda nokta işaretinden hemen önce köşeli parantez kullanılarak belirtilmelidir. Örneğin [4,5]. Kaynakların doğruluğundan yazar(lar) sorumludur. Yerli ve yabancı kaynakların sentezine önem verilmelidir.

Şekil ve tablo başlıkları: Başlıklar kaynaklardan sonra yazılmalıdır.

4. Şekiller: Her biri ayrı bir görüntü dosyası (jpg) olarak gönderilmelidir.

Makalenin basıma kabulünden sonra "Dizginin ilk düzeltme nüshası" sorumlu yazara e-mail yoluyla gönderilecektir. Bu metinde sadece yazım hataları düzeltilecek, ekleme çıkartma yapılmayacaktır. Sorumlu yazar düzeltmeleri 2 gün içinde bir dosya halinde e-mail ile yayın idare merkezine bildirecektir.

Kaynak Yazım Örnekleri

Dergilerden yapılan alıntı;

Özpolat B, Gürpınar ÖA, Ayva EŞ, Gazyağcı S, Niyaz M. The effect of Basic Fibroblast Growth Factor and adipose tissue derived mesenchymal stem cells on wound healing, epithelization and angiogenesis in a tracheal resection and end to end anastomosis rat model. Turk Gogus Kalp Dama 2013; 21: 1010-19.

Kitaptan yapılan alıntı;

Tos M. Cartilage tympanoplasty. 1st ed. Stuttgart-New York: Georg Thieme Verlag; 2009.

Tek yazar ve editörü olan kitaptan alıntı;

Neinstein LS. The office visit, interview techniques, and recommendations to parents. In: Neinstein LS (ed). Adolescent Health Care. A practical guide. 3rd ed. Baltimore: Williams&Wilkins; 1996: 46-60.

Çoklu yazar ve editörü olan kitaptan alıntı;

Schulz JE, Parran T Jr: Principles of identification and intervention. In:Principles of Addicton Medicine, Graham AW. Shultz TK (eds). American Society of Addiction Medicine, 3rd ed. Baltimore: Williams&Wilkins; 1998:1-10.

Eğer editör aynı zamanda kitap içinde bölüm yazarı ise;

Diener HC, Wilkinson M (editors). Drug-induced headache. In: Headache. First ed., New York: Springer-Verlag;1988:45-67.

Doktora/Lisans Tezinden alıntı;

Kılıç C. General Health Survey: A Study of Reliability and Validity. phD Thesis, Hacettepe University Faculty of Medicine, Department of Psychiatrics, Ankara; 1992.

Bir internet sitesinden alıntı;

Sitenin adı, URL adresi, yazar adları, ulaşım tarihi detaylı olarak verilmelidir.

DOI numarası vermek;

Joos S, Musselmann B, Szecsenyi J. Integration of Complementary and Alternative Medicine into Family Practice in Germany: Result of National Survey. Evid Based Complement Alternat Med 2011 (doi: 10.1093/ecam/nep019).

Diğer referans stilleri için "ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Sample References" sayfasını ziyaret ediniz.

Bilimsel sorumluluk beyanı: Kabul edilen bir makalenin yayınlanmasından önce her yazar, araştırmaya, içeriğinin sorumluluğunu paylaşmaya yetecek boyutta katıldığını beyan etmelidir. Bu katılım şu konularda olabilir:

a. Deneylerin konsept ve dizaynlarının oluşturulması, veya verilerin toplanması, analizi ya da ifade edilmesi;

b. Makalenin taslağının hazırlanması veya bilimsel içeriğinin gözden geçirilmesi

c. Makalenin basılmaya hazır son halinin onaylanması.

Yazının bir başka yere yayın için gönderilmediğinin beyanı: "Bu çalışmanın içindeki materyalin tamamı ya da bir kısmının daha önce herhangi bir yerde yayınlanmadığını, ve halihazırda da yayın için başka bir yerde değerlendirilmede olmadığını beyan ederim. Bu, 400 kelimeye kadar olan özetler hariç, sempozyumlar, bilgi aktarımları, kitaplar, davet üzerine yazılan makaleler, elektronik formatta gönderimler ve her türden ön bildirileri içerir."

Sponsorluk beyanı: Yazarlar aşağıda belirtilen alanlarda, varsa çalışmaya sponsorluk edenlerin rollerini beyan etmelidirler:

1. Çalışmanın dizaynı

2. Veri toplanması, analizi ve sonuçların yorumlanması

3. Raporun yazılması

Kontrol listesi:

1. Editöre sunum sayfası (Sorumlu yazar tarafından yazılmış olmalıdır)

2. Başlık sayfası (Makale başlığı/kısa başlık Türkçe ve İngilizce, Yazarlar, kurumları, sorumlu yazar posta adresi, tüm yazarların e-mail adresleri, sorumlu yazarın telefon numarası)

3. Makalenin metin sayfası (Makale başlığı/kısa başlık Türkçe ve İngilizce, Özet/anahtar kelimeler, Summary/keywords, makale metni, kaynaklar, tablo ve şekil başlıkları, tablolar, şekiller)

4. Tablo ve grafikler metin içinde olmalıdır.

5. Şekiller (En az 300 dpi çözünürlükte) ayrı bir veya daha fazla dosya halinde gönderilmelidir.

TURKISH JOURNAL of CLINICS and LABORATORY

Türk Klinik ve Laboratuvar Dergisi

Turkish Journal of Clinics and Laboratory - Türk Klinik ve Laboratuvar Dergisi

Tıp dergilerine gönderilecek makalelerin standart gereksinmeleri ile ilgili tüm bilgileri www.icmje.org internet adresinde bulabilirsiniz

Amaç ve kapsam: "Turkish Journal of Clinics and Laboratory", hakemli, açık erişimli ve periyodik olarak çıkan, DNT Ortadoğu Yayıncılık A.Ş. ye ait bir dergidir. Hedefimiz uluslararası bir tabanda hastalıkların teşhis ve tedavisinde yenilikler içeren yüksek kalitede bilimsel makaleler yayınlamaktır. Yılda dört kez çıkan bir bilimsel bir tıp dergisidir. Hakemli bir dergi olarak gelen yazılar konsültanlar tarafından, öncelikle, biyomedikal makalelere ait Uluslararası Tıp Dergileri Editörleri Komitesi (www.icmje.org adresinden ulaşılabilir) tarafından tanımlanan standart gereksinimler ile ilgili ortak kurallara uygunluğu açısından değerlendirilir. Tıbbın her dalı ile ilgili retrospektif/prospektif klinik ve laboratuar çalışmalar, ilginç olgu sunumları, davet üzerine yazılan derlemeler, editöre mektuplar, orijinal görüntüler, kısa raporlar ve cerrahi teknik yazılarıları yayımlayan bilimsel, uluslar arası hakemli bir dergidir. Başka bir dergide yayımlanmış veya değerlendirilmek üzere gönderilmiş yazılar veya dergi kurallarına göre hazırlanmamış yazılar değerlendirme için kabul edilmez.

On-line makale gönderimi: Tüm yazışmalar ve yazı gönderimleri dergipark üzerinden http://dergipark.gov.tr/tjcl yapılmalıdır. Yazı gönderimi için detaylı bilgi bu internet adresinden edinilebilir. Gönderilen her yazı için özel bir numara verilecek ve yazının alındığı e-posta yolu ile teyid edilecektir. Makalelerin "full-text" pdf formuna http://dergipark.gov.tr/tjcl linkinden ulaşılabilir.

Açık erişim politikası: Turkish Journal of Clinics and Laboratory açık erişimi olan bir dergidir. Kullanıcı lar yazıların tam metnine ulaşabilir, kaynak gösterilerek tüm makaleler bilimsel çalışmalarda kullanılabilir.

Aşağıdaki rehber dergiye gönderilen makalelerde aranan standartları göstermektedir. Bu uluslararası format, makale değerlendirme ve basım aşamalarının hızla yapılmasını sağlayacaktır.

Yazarlara Bilgi: Yazıların tüm bilimsel sorumluluğunu yazar(lar)a aittir. Editör, yardımcı editör ve yayıncı dergide yayınlanan yazılar için herhangi bir sorumluluk kabul etmez.

Dergi adının kısaltması: Turk J Clin Lab

Yazışma adresi: Yazılar e-mail yoluyla sorumlu yazar tarafından, Dergipark ta yer alan Turkish Journal of Clinics and Laboratory linkine girip kayıt olduktan sonra gönderilmelidir.

Makale dili: Makale dili Türkçe ve İngilizcedir. İngilizce makaleler gönderilmeden önce profesyonel bir dil uzmanı tarafından kontrol edilmelidir. Yazıdaki yazım ve gramer hataları içerik değişmeyecek şekilde İngilizce dil danışmanı tarafından düzeltilebilir. Türkçe yazılan yazılarda düzgün bir Türkçe kullanımı önemlidir. Bu amaçla, Türk Dil Kurumu Sözlük ve Yazım Kılavuzu yazım dilinde esas alınmalıdır.

Makalenin başka bir yerde yayımlanmamıştır ibaresi: Her yazar makalenin bir bölümünün veya tamamının başka bir yerde yayımlanmadığını ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığını, editöre sunum sayfasında belirtmelidirler. 400 kelimeden az özetler kapsam dışıdır. Kongrelerde sunulan sözlü veya poster bildirilerin, başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmesi gereklidir. Dergide yayımlanan yazıların her türlü sorumluluğu (etik, bilimsel, yasal, vb.) yazarlara aittir.

Değerlendirme: Dergiye gönderilen yazılar format ve plagiarism açısından değerlendirilir. Formata uygun olmayan yazılar değerlendirilmeden sorumlu yazara geri gönderilir. Bu tarz bir zaman kaybının olmaması için yazım kuralları gözden geçirilmelidir. Basım için gönderilen tüm yazılar iki veya daha fazla yerli/yabancı hakem tarafından değerlendirilir. Makalelerin değerlendirilmesi, bilimsel önemi, orijinalliği göz önüne alınarak yapılır. Yayıma kabul edilen yazılar editörler kurulu tarafından içerik değiştirilmeden yazarlara haber verilerek yeniden düzenlenebilir. Makalenin dergiye gönderilmesi veya basıma kabul edilmesi sonrası isim sırası değiştirilemez, yazar ismi eklenip çıkartılamaz.

Basıma kabul edilmesi: Editör ve hakemlerin uygunluk vermesi sonrası makalenin gönderim tarihi esas alınarak basım sırasına alınır. Her yazı için bir doi numarası alınır.

Yayın hakları devri: http:/www.dergipark.ulakbim.gov.tr/tjclinlab adresi üzerinden online olarak gönderilmelidir. 1976 Copyright Act'e göre, yayımlanmak üzere kabul edilen yazıların her türlü yayın hakkı yayıncıya aittir.

Makale genel yazım kuralları: Yazılar Microsoft Word programı (7.0 ve üst versiyon) ile çift satır aralıklı ve 12 punto olarak, her sayfanın iki yanında ve alt ve üst kısmında 2,5 cm boşluk bırakılarak yazılmalıdır. Yazı stili Times New roman olmalıdır. "System International" (SI) unitler kullanılmalıdır. Şekil tablo ve grafikler metin içinde refere edilmelidir. Kısaltmalar, kelimenin ilk geçtiği yerde parantez içinde verilmelidir. Türkçe makalelerde %50 bitişik yazılmalı, aynı şekilde İngilizcelerde de 50% bitişik olmalıdır. Türkçede ondalık sayılarda virgül kullanılmalı (55,78) İngilizce yazılarda nokta (55.78) kullanılmalıdır. Derleme 4000, orijinal çalışma 2500, olgu sunumu 1200, editöre mektup 500 kelimeyi geçmemelidir. Özet sayfasından sonraki sayfalar numaralandırılmalıdır.

Yazının bölümleri

1. Sunum sayfası: Yazının Turkish Journal of Clinics and Laboratory 'de yayınlanmak üzere değerlendirilmesi isteğinin belirtildiği, makalenin sorumlu yazarı tarafından dergi editörüne hitaben gönderdiği yazıdır. Bu kısımda makalenin bir bölümünün veya tamamının başka bir yerde yayımlanmadığını ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığını, maddi destek ve çıkar ilişkisi durumu belirtmelidir.

2. Başlık sayfası: Sayfa başında gönderilen makalenin kategorisi belirtilmedir (Klinik analiz, orijinal çalışma, deneysel çalışma, olgu sunumu vs).

Başlık: Kısa ve net bir başlık olmalıdır. Kısaltma içermemelidir. Türkçe ve İngilizce yazılmalı ve kısa başlık (runing title) Türkçe ve İngilizce olarak eklenmelidir. Tüm yazarların ad ve soyadları yazıldıktan sonra üst simge ile 1'den itibaren numaralandırılıp, unvanları, çalıştıkları kurum, klinik ve şehir yazar isimleri altına eklenmelidir.

Bu sayfada "sorumlu yazar" belirtilmeli isim, açık adres, telefon ve e-posta bilgileri eklenmelidir.

Kongrelerde sunulan sözlü veya poster bildirilerin, başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmesi gereklidir.

3. Makale dosyası: (Yazar ve kurum isimleri bulunmamalıdır)

Başlık: Kısa ve net bir başlık olmalıdır. Kısaltma içermemelidir. Türkçe ve İngilizce yazılmalı ve kısa başlık (runing title) Türkçe ve İngilizce olarak eklenmelidir.

Özet: Türkçe ve İngilizce yazılmalıdır. Orijinal çalışmalarda özetler, Amaç (Aim), Gereç ve Yöntemler (Material and Methods), Bulgular (Results) ve Sonuçlar (Conclusion) bölümlerine ayrılmalı ve 250 sözcüğü geçmemelidir. Olgu sunumları ve benzerlerinde özetler, kısa ve tek paragraflık olmalıdır (150 kelime), Derlemelerde 300 kelimeyi geçmemelidir.

Anahtar kelimeler: Türkçe ve İngilizce özetlerin sonlarında bulunmalıdır. En az 3 en fazla 6 adet yazılmalıdır. Kelimeler birbirlerinden noktalı virgül ile ayrılmalıdır. İngilizce anahtar kelimeler "Medical Subject Headings (MESH)" e uygun olarak verilmelidir. (www.nlm.nih.gov/mesh/MBrowser.html). Türkçe anahtar kelimeler "Türkiye Bilim Terimleri' ne uygun olarak verilmelidir (www.bilimterimleri.com). Bulunamaması durumunda birebir Türkçe tercümesi verilmelidir.

Metin bölümleri: Orijinal makaleler; Giriş, Gereç ve Yöntemler, Bulgular, Tartışma olarak düzenlenmelidir. Olgu sunumları; Giriş, Olgu sunumu, Tartışma olarak düzenlenmelidir. Şekil, fotoğraf, tablo ve grafiklerin metin içinde geçtiği yerler ilgili cümlenin sonunda belirtilmeli metin içine yerleştirilmemelidir. Kullanılan kısaltmalar altındaki açıklamada belirtilmelidir. Daha önce basılmış şekil, resim, tablo ve grafik kullanılmış ise yazılı izin alınmalıdır ve bu izin açıklama olarak şekil, resim, tablo ve grafik açıklamasında belirtilmelidir. Tablolar metin sonuna eklenmelidir. Resimler/fotoğraf kalitesi en az 300dpi olmalıdır.