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Table of Contents

Original Articles

Assessment of thrombin-activatable fibrinolysis inhibitor levels in essential hypertension 1-10
Ayla YILDIZ, Kerem OKUTUR, Nezaket EREN

Investigation of the relationship between prolactin and infertility by expression levels of kisspeptin (KISS1), KISS1 receptor, neurokinin (NK), NK receptor genes 11-18
Eylül AKBAL, Mehmet Bertan YILMAZ

Is prostate-specific antigen density superior than prostate-specific antigen kinetics and prostate volume in predicting clinically insignificant prostate cancer? 19-26
Sinan AVCI, Özgür EKİCİ, Volkan ÇAĞLAYAN, Abdullah ERDOĞAN, Efe ÖNEN, Uğur AKGÜN, Rıdvan ÖZCAN, Sedat ÖNER

Effect of transdermally applied nitroglycerin or lidocaine before transradial coronary angiography on procedure success and complications 27-33
Nurullah USLU, Cihan AYDIN, Aykut DEMİRKIRAN, Hüseyin AYKAÇ, Şeref ALĞSOY

A different training model in providing effective medical waste management in the operating room: peer education 34-42
Nuran AKINCI EKİNCİ, Mehmet Akif YAZAR, Betül KOZANHAN, Sami UYAR

Clinical and electrocardiographic predictors of left ventricular diastolic dysfunction in patients with idiopathic premature ventricular contractions 43-50
Onur KAYPAKLI, Fatma Özge SALKIN

Evaluation of bismuth shielding in reducing thyroid radiation dose during neck multidetector computed tomography examinations: a comparative study 51-56
Yeliz BAŞAR

Identification of needs of family members of surgical intensive care unit patients: a cross-sectional study 57-67
İsmail ÖZTAŞ, Ayla YAVA, Aynur KOYUNCU, Sema KAPTANOĞLU

Comparative analysis of purse-string method versus conventional methods for stoma closure 68-73
Amil HÜSEYNOV, Veli VURAL

Myotonia may be a sign that prompts genetic testing for myotonic dystrophy type 1 74-79
Metin ESER , Gulam HEKİMOĞLU, Büşra KUTLUBAY

Increasing cumulative cabergoline dose in patients with prolactinoma improves metabolic parameters independently of decrease in prolactin levels 80-87
Ahmet Numan DEMİR, Alara BİROL, Dilan ÖZAYDIN, Serdar ŞAHİN , Pınar KADIOĞLU

Diagnostic performance of ultrasound versus 99mTc-sestamibi scintigraphy in preoperative depiction and localization of parathyroid adenoma in patients with primary hyperparathyroidism 88-97
Ercüment GÜRLÜER

Corneal topographic and aberrometric changes in patients with acquired blepharoptosis after levator resection surgery 98-104
Ayna SARİYEVA ISMAYİLOV, Derya DOĞANAY, Muhammed YELKOVAN

Correlation of radiological and histopathological findings in the diagnosis of benign bone tumors 105-112
Berna ERİTEN , Serdar MENEKŞE

Review

Analysis of skin health management through telemedicine and mobile health in dermatology in the post-COVID era 113-122
Şule GENÇOĞLU

Therapeutic approaches to language skills in major neurodegenerative disorders: a literature review 123-128
Fenise Selin KARALI, Samet TOSUN, Nilgün ÇINAR

Case Report

Clinical and genetic diagnosis of two Turkish patients with hereditary spherocytosis 129-134
Çağrı COŞKUN

The European Research Journal 2025;11(1):1-10 Original Article

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Assessment of thrombin-activatable fibrinolysis inhibitor levels in essential hypertension

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ABSTRACT

Objectives: Most research in this field has highlighted the significance of the fibrinolytic system in essential hypertension, revealing anomalies within the coagulation and fibrinolytic pathways that contribute to a hypercoagulable condition. We aim to investigate thrombin-activatable fibrinolysis inhibitor (TAFI) levels in individuals diagnosed with high blood pressure.

Methods: We compared 40 newly diagnosed cases of essential hypertension, who were not receiving antihypertensive medication, with 40 normotensive individuals as controls. Various parameters and TAFI levels were assessed in all subjects and compared between the groups. Additionally, hypertensive patients were classified based on whether they exhibited high or normal cholesterol levels (≥200 mg/dL).

Results: The concentrations of TAFI were significantly higher in the hypertensive cohort compared to the normotensive counterparts (116.95±29.76 and 77.72±32.78 (ng/mL) , respectively; P<0.001). In addition, the high blood pressure cohort exhibited a notably higher mean body mass index (BMI) in contrast to the normotensive group (29.55±4.82 vs. 24.93±3.07 kg/m2, respectively; P<0.001). On the other hand, the remaining results showed no statistically significant differences between the two cohorts. Linear regression analysis revealed that blood pressure status and BMI independently correlated with plasma TAFI levels.

Conclusions: The concentrations of TAFI are elevated in patients with high blood pressure compared to individuals with normal blood pressure, irrespective of high cholesterol levels. Further exploration is necessary to clarify the involvement of TAFIs in the pathophysiology of primary hypertension, necessitating advanced investigatory initiatives.

Keywords: Thrombin activatable fibrinolysis inhibitor, cardiovascular diseases, thrombosis, fibrinolysis

Essential hypertension (PHT) accounts for 85-90% of all cases of hypertension. Hypertension represents a substantial risk factor for cardiovascular diseases, which stand as the foremost cause of mortality globally. The asymptomatic presentation of primary hypertension frequently results in diagnostic delays and unfavorable cardiovascular consequences [1]. Additionally, it induces abnormalities in the coagulation and fibrinolytic systems, leading to disruption in the balance of coagulation [2]. Thrombin-activatable fibrinolysis Inhibitor (TAFI) has garnered growing attention in recent years regarding its

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implications for the interplay among atherosclerosis, hypertension, and hemostasis. Moreover, it belongs to the group of metalloproteinases, acting as a proenzyme for carboxypeptidase. TAFI is activated by thrombin, leading to the inhibition of fibrin degradation, which is essential for preserving the delicate equilibrium between fibrinolysis and coagulation [3-5]. In addition, circulating concentrations of this marker are elevated in pathologies which characterized by hypercoagulability. Hypertension (HT) represents a predisposing factor for the majority of these conditions [6].

In addition to its role in coagulation/fibrinolysis and inflammatory processes, some studies suggest a potential association between plasma TAFI levels and hyperlipidemia. Some studies have shown that Low low-density lipoprotein cholesterol (LDL) is a significant determinant of plasma TAFI in studies involving individuals with type 2 diabetes [7].

In previous studies, researchers observed that women diagnosed with hypercholesterolemia showed markedly elevated TAFI levels compared to women without this risk factor, while exploring the correlation between our markers and traditional cardiovascular risk factors [8].

In subsequent scientific studies demonstrating the effects of simvastatin treatment, it was observed that TAFI levels decreased significantly following simvastatin therapy [9].

Based on these findings, it is suggested that due to the biochemical properties of TAFI, it could influence the relationship between hyperlipidemia and PHT. Therefore, additional research is necessary. Consequently, we examined TAFI levels in patients diagnosed with PHT and hypercholesterolemia and meticulously controlled prospective clinical trials.

METHODS

The study involved 40 individuals newly diagnosed with primary hypertension and the same number of control groups. Primary hypertension was characterized by blood pressure (BP) readings ≥140/90 mmHg, without an identifiable secondary cause [10].

The exclusion criteria included kidney diseases, endocrine disorders, diabetes, and antilipidemic medication users. This thesis was conducted at Istanbul Şişli Hamidiye Etfal Training and Research Hospital.

Comprehensive clinical patient information including medication usage was obtained. The body mass index (BMI) of the individuals was determined through measurements of their height and weight.

Blood samples were obtained from participants following a 12-hour overnight fasting period. Serum was collected into tubes with a gel separator, while plasma was collected into tubes containing 3.2% trisodium citrate solution as a blood thinner. The biological materials were centrifuged according to the protocol, aliquoted, and stored at -80°C. Lipid profile tests and C-reactive protein (CRP) serum levels were conducted using the Abbott-Aeroset automated analyzer at Abbott Diagnostics, Illinois, USA.

Fibrinogen, as one of the coagulation tests, was assessed using the Clauss method on the ACL Advance automated analyzer (San Diego, Instrumentation Laboratory, USA). The concentrations of TAFI antigen used as a research kit were measured using an enzyme-linked immunosorbent assay (ELISA) kit. (American Diagnostica Inc Imunclone, USA). The group diagnosed with primary hypertension and the normotensive group were also divided into two groups based on high cholesterol levels (total cholesterol levels ≥ 200 mg/dL and those < 200 mg/dL). As a result, our study continued with four groups based on these criteria.

Statistical Analysis

It was conducted using the SPSS 22.0 software package. Descriptive statistics including mean and standard deviation were presented for normally distributed numerical variables. Normality of variables was assessed visually using histogram and probability graphs, as well as analytically using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Student's t-test and One-Way ANOVA were employed for comparisons between two groups and multiple groups, respectively. For variables that did not follow a normal distribution, median, interquartile range (IQR), minimum, and maximum values were reported, and the Mann-Whitney U test was used for comparisons between the two groups. Statistical remarkable levels were defined as ($P<0.050$). Linear regression analysis was utilized to independent variables associated with TAFI antigen concentration. Pearson correlation analysis was applied to parameters showing homogeneous distribu-

tion, while Spearman correlation analysis was used for parameters not showing homogeneous distribution. The statistical power of the study was computed using this software [11]. The study's statistical power was determined to be 0.80, with a significance level (α) of 0.05 and a power of 80% (β=0.20). In our study, a Type II error rate of 20% and a Type I error rate of 0.05 with a 95% confidence interval were chosen to achieve 80% statistical power. The sample size was calculated using information from a previous study, where the average TAFI levels were reported as 104.91±27.43 (ng/mL) in the group with high blood pressure and 87.59±25.82 (ng/mL) in the group without high blood pressure.

RESULTS

The basic clinical features and biochemical tests of the hypertensive and normotensive groups are presented in Table 1. While statistically significant differences were observed in BMI, CRP, and TAFI levels, no differences were found between the two groups in most lipid profile and coagulation parameters, fibrinogen. (Table 1). Moreover, TAFI antigen did not significantly differ between hypercholesterolemic and normocholesterolemic patients (98.5±37.1 and 95.1± 37.0 (ng/mL), respectively; P=0.570)). Similarly, there was no remarkable disparity in TAFI levels based on hypertensive and normotensive groups. After dividing the two groups into subgroups based on high cholesterol levels (<200 mg/dL and ≥200 mg/dL), we compared the TAFI levels between these subgroups. Analysis revealed no statistically significant differences in TAFI levels among the subgroups of both hypertensive and normotensive individuals categorized by total cholesterol levels (P=0.471 and P=0.839, respectively) (Fig. 1). Table 2 provides a detailed overview of the linear regression analysis findings related to the factors associated with serum TAFI levels. The data indicate that TAFI levels are independently associated with both BMI and essential hypertension. In our study, correlation analysis revealed a positive and significant relationship between age and BMI (r=0.267, P=0.017); TAFI and BMI (r=0.455, P<0.001); age and CRP (r=0.349, P=0.002); and fib-

Table 1. Demographic characteristics and biochemical parameters of cases

	Hypertensive group (n=40)	Normotensive group (n=40)	P value
Systolic blood pressure (mmHg)	161.87±16.43	116.02±4.84	**<0.001**
Diastolic blood pressure (mmHg)	100.62±11.44	75.12±6.25	**<0.001**
Age (year)	47±7.57	46.15±4.31	0.539
Weight (kg)	77.35±12.84	68.75±10.37	**0.001**
Height (cm)	162.88±9.03	166.38±7.50	0.063
BMI (kg/m^2)	29.55±4.82	24.93±3.07	**<0.001**
Total cholesterol (mg/dL)	195.20±37.91	194.27±41.55	0.917
Triglyceride (mg/dL)	122±54	127±88	0.516
HDL cholesterol (mg/dL)	43.8±9.7	42.2±11.9	0.512
LDL cholesterol (mg/dL)	126.50±32.69	126.24±36.96	0.973
Fibrinogen (mg/dL)	328.35±60.67	328.72±65.59	0.979
TAFI (ng/mL)	116.95±29.76	77.72±32.78	**<0.001**
CRP (mg/dL) *	3.14±2.72 (0.01-25.70)	2.17±3.56 (0.01-24.00)	**0.030**

All parameters were shown as mean ± standard deviation. *CRP values are shown as median (Interquartile range) (minimum-maximum). TAFI=Thrombin-Activatable Fibrinolysis Inhibitor, BMI=Body Mass Index, HDL=High Density Lipoprotein, LDL=Low Density Lipoprotein, CRP=C-Reactive Protein

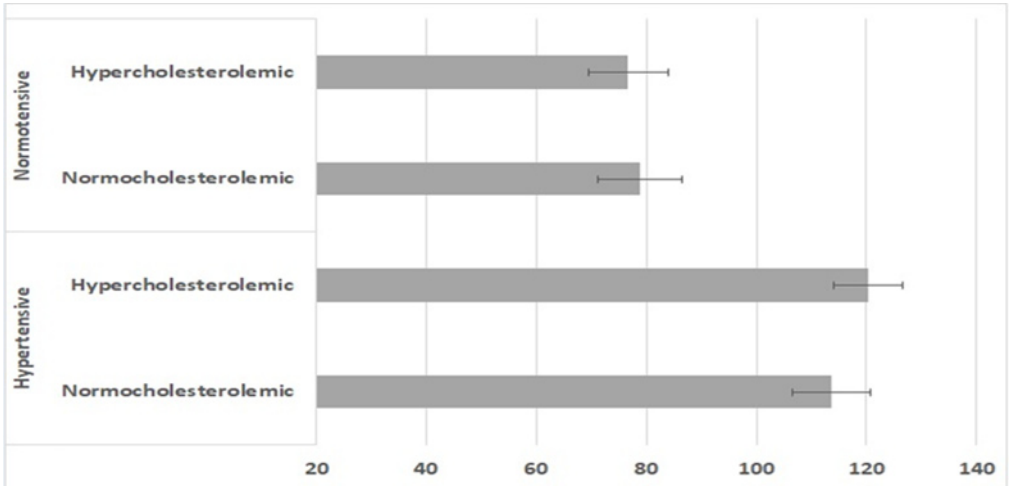

Fig. 1. Serum TAFI levels (ng/mL); TAFI=Thrombin-Activatable Fibrinolysis Inhibitor.

rinogen and CRP (r=0.386, P<0.001). No significant relationship was found among other biochemical parameters (Table 3).

DISCUSSION

The objective of this investigation was to assess TAFI levels in individuals with PHT who had not undergone any antihypertensive treatments. Upon comparison between the hypertensive and normotensive groups, it was observed that our markers were notably increased in the hypertensive group (Table 1). Additionally, the hypertensive group exhibited significantly higher BMI and CRP values compared to the normotensive group.

The main goal of the current study was to determine TAFI Antigen concentrations in individuals diagnosed with PHT who had not undergone any antihypertensive interventions. Upon comparison between the hypertensive and normotensive cohorts, it

Table 2. Linear regression analyses of the parameters related to TAFI levels

	B	P value	95% CI for B	
			Lower bound	Upper bound
(Constant)	71.443	0.139	-23.704	166.591
Age (year)	-0.833	0.173	-2.041	0.375
Gender (female/male)	-3.494	0.665	-19.500	12.512
Groups (normotensive/hypertensive/)	-28.739	**0.001**	-44.764	-12.715
BMI (kg/m^2)	2.173	**0.023**	0.306	4.041
HDL cholesterol(mg/dL)	0.338	0.345	-0.371	1.047
LDL cholesterol(mg/dL)	0.001	0.994	-0.217	0.218
Triglyceride(mg/dL)	0.048	0.335	-0.051	0.147
Fibrinogen(mg/dL)	0.094	0.194	-0.049	0.237
CRP (mg/dL)*	-0.322	0.732	-2.192	1.548

TAFI=Thrombin-Activatable Fibrinolysis Inhibitor, BMI=Body Mass Index, HDL=High Density Lipoprotein, LDL=Low Density Lipoprotein, CRP=C-Reactive Protein, OR=Odds ratio, CI=confidence interval

*P value=0.030

Table 3. **Correlation analysis of the parameters**

		Age (year)	BMI (kg/m^2)	HDL cholesterol (mg/dL)	LDL cholesterol (mg/dL)	Triglyceride (mg/dL)	Fibrinogen (mg/dL)	TAFI (ng/mL)
Age (year)	r		0.267*	-0.042	0.124	0.15	-0.126	-0.04
	P value		**0.017**	0.714	0.272	0.184	0.266	0.724
BMI (kg/m^2)	r	0.267*		0.072	0.064	0.128	0.05	0.455*
	P value	**0.017**		0.528	0.571	0.257	0.658	**<0.001**
HDL cholesterol (mg/dL)	r	-0.042	0.072		0.124	-0.069	-0.075	0.166
	P value	0.714	0.528		0.274	0.542	0.51	0.14
LDL cholesterol (mg/dL)	r	0.124	0.064	0.124		0.02	0.208	0.024
	P value	0.272	0.571	0.274		0.862	0.064	0.832
Triglyceride (mg/dL)	r	0.15	0.128	-0.069	0.02		0.008	0.07
	P value	0.184	0.257	0.542	0.862		0.941	0.539
Fibrinogen (mg/dL)	r	-0.126	0.05	-0.075	0.208	0.008		0.107
	P value	0.266	0.658	0.51	0.064	0.941		0.344
TAFI (ng/mL)	r	-0.04	0.455*	0.166	0.024	0.07	0.107	
	P value	0.724	**<0.001**	0.14	0.832	0.539	0.344	
CRP (mg/dL)**	r	0.095	0.349*	-0.115	-0.099	0.168	0.386	0.141
	P value	0.403	**0.002**	0.309	0.382	0.137	**<0.001**	0.211

TAFI=Thrombin-Activatable Fibrinolysis Inhibitor, BMI=Body Mass Index, HDL=High Density Lipoprotein, LDL=Low Density Lipoprotein, CRP=C-Reactive Protein, r=Pearson correlation coefficient, rs=Spearman correlation coefficient

*Correlation is significant at the 0.05 level

**Spearman Correlation Analysis

was observed that the TAFI levels in the hypertensive group were markedly elevated, as delineated in Table 1. Additionally, the hypertensive cohort exhibited notably higher BMI and CRP values in contrast to the normotensive group. Within this dataset, linear regression analyses were conducted to explore the factors associated with TAFI Antigen, aiming to ascertain whether TAFI elevation in the hypertensive cohort remained independent of BMI and CRP concentrations (Table 2), which were notably elevated within this group. Essentially, the rise in TAFI levels among hypertensive individuals was determined to be linked to hypertension status, irrespective of BMI and CRP values (Table 2).

Based on the correlation analysis performed in our study, a statistically significant positive association was identified between CRP and both age and fibrinogen levels. Additionally, a significant positive correlation was observed BMI and age, as well as between BMI and TAFI levels.

Multiple pathways might elucidate the heightened TAFI levels observed in PHT patients. Animal studies indicate TAFI's expression as an acute-phase protein [12]. Furthermore, this antigen elicits inflammatory and coagulation cascades [13, 14]. Anticoagulation play a role in decreasing inflammation, as inflammatory conditions can lead to blood clot formation. Moreover, research shows that higher levels of TAFI are linked to markers of endothelial cell damage, such as thrombin-antithrombin complexes and thrombomodulin. This suggests a relationship between inflammation, endothelial damage, and the risk of clot formation [15]. The presence of inflammation-induced endothelial dysfunction exacerbates the susceptibility to thrombotic events in individuals diagnosed with pulmonary hypertension disease [16]. Elevated levels of TAFI, originating from endothelial sources, may escalate due to endothelial damage, consequently fostering a state of hypercoagulability [17]. These observations align with numerous studies within the existing literature.

In prior research on renal transplant recipients, Malyszko *et al*. found that hypertensive patients had increased levels of TAFI compared to those with normal blood pressure [18].

Furthermore, they noted a relationship between the increase in TAFI and levels of the thrombin-antithrombin (TAT) complex, linking it to vascular endothelial injury observed in the hypertensive group. This endothelial damage led to increased TAT levels, subsequently promoting the formation of TAT complexes, which in turn heightened TAFI levels. Another investigation involving 72 hypertensive patients reported elevated levels of both TAFI and TAT, mutually reinforcing their relationship [18].

In our study, we observed increased TAFI levels among hypertensive patients, while levels of Activated Partial Thromboplastin Time (aPTT), fibrinogen, Prothrombin time (PT), TAT, and d-dimer remained unchanged. Therefore, we concluded that the increase in TAFI occurred independently of coagulation cascade activation. Özkan *et al*. [19] investigated the link between hypertension and fibrinolysis anomalies. Their study, which included 58 hypertensive subjects and 27 controls, revealed significantly elevated TAFI levels in the hypertensive group (P=0.03). Following one month of antihypertensive therapy, a statistically significant reduction in TAFI levels was observed (P=0.037). These results agree with the findings of our studies, in which illustrate a positive correlation between essential hypertension and TAFI Antigen concentrations.

According to Santos *et al*. [20] the crucial role of dyslipidemia as a major risk factor for atherosclerosis and coronary artery disease. It was observed that dyslipidemia negatively impacts the hemostatic system, resulting in impaired fibrinolysis and a subsequent increase in TAFI levels during cardiovascular conditions. Unlike their research focused on examining the association among clinical risk factors" (such as hypertension, BMI, smoking, etc.), gene polymorphisms (Alanin 147Thr (rs3742264), Threonin 325Ile (rs1926447) in the TAFI gene, and +1542C/G (rs940)) biochemical parameters and TAFI levels in 105 normolipidemic and 109 dyslipidemic cases. They found significantly elevated TAFI levels in dyslipidemic individuals with concurrent hypertension, increased BMI, and postmenopausal status. Additionally, certain alleles (Alanin 147, 325 Izolosin and C) were associated with lower TAFI levels, and the polymorphism rs3742264 was linked to dyslipidemia in male patients. Hence, the observation of elevated TAFI levels irrespective of dyslipidemia in their study corroborates our findings [20]. Additionally, our study found a significant relationship between BMI and TAFI, which supports the findings of the current study.

In another study, Santamaria *et al*. [8] compared TAFI levels with various hemostatic parameters such as FXII, Protein C, Fibrinogen, t-PA, and von Willebrand Factor, considering age and gender. Contrary to our findings, they did not find a significant difference between TAFI levels and hemostatic parameters. However, they observed significantly lower TAFI levels in female patients under the age of 30 as a notable finding. Moreover, they in female patients diagnosed with hypercholesterolemia. In addition, they conducted their study specifically on female patients with hypercholesterolemia. In our prospective study, TAFI levels were measured without grouping by age. We focused solely on age and gender to maintain group homogeneity. Our findings revealed significantly higher TAFI Antigen levels in patients with PHT compared to normotensive individuals (P<0.01). There was no statistically significant difference in TAFI and fibrinogen levels between the two groups (P>0.050).

In this comprehensive analysis, we exclusively quantified TAFI Antigen concentrations. Several investigations have found a correlation between circulating TAFI activity (TAFIa) and TAFI antigen concentrations [21, 22].

Although multiple investigations have identified a substantial correlation between TAFI levels and hypercholesterolemia, our study demonstrated that the elevation in TAFI levels among hypertensive patients occurred regardless of lipid level [6, 23, 24].
Yoshimasa *et al*. [23] investigated 136 participants diagnosed with type 2 diabetes. As a result, they did not find a statistically significant difference between metabolic parameters such as hs-CRP, insulin resistance, lipid levels, BMI, and PAI-1 level. Significantly, they observed that plasma TAFI levels correlated positively only with LDL cholesterol. Although they found a reverse correlation with Plasminogen Activator Inhibitor 1 (PAI-1), the level of alpha-2 antiplasmin did not show a corresponding negative correlation with TAFI. In conclusion, they highlighted the importance of assessing LDL cholesterol levels when examining TAFI in patients diagnosed with Type II diabetes mellitus. They emphasized the significance of the combined impact of metabolic syndrome and hypercholesterolemia, stating that it accelerates inflammatory processes. Additionally, they demonstrated a significant correlation between impaired fibrinolysis and elevated levels of PAI-1 and TAFI. Despite these outcomes, our study did not identify a statistically significant difference between TAFI and LDL cholesterol (P>0.05).

Elevated TAFI levels (near 126%) were associated with nearly a fourfold increase in the likelihood of acute coronary artery disease (CAD). Moreover, heightened TAFI levels have been linked to a substantial rise the probability of ischemic stroke and represent a considerable risk factor for coronary artery disease [25]. Previous studies have shown an increase in TAFI concentrations in individuals with stable angina pectoris and coronary artery disease identified via angiography [26]. It has been pointed out that elevated TAFI levels observed in metabolic syndrome contribute to the inhibition of fibrinolysis and accelerate disease progression [26, 27].
Unlike the earlier studies referenced, our research revealed no significant difference in triglyceride (P>0.05), LDL-cholesterol (P>0.05), and total cholesterol (P>0.05) levels between hypertensive and normotensive groups. This discovery led us to propose that the rise in TAFI levels could be directly caused by PHT.

Recent researches have shown that TAFIa serves as a promising target for addressing thromboembolic disorders. Presently, several studies are underway to develop TAFIa inhibitors for thrombosis treatment. However, no TAFIa inhibitor drug has been developed for clinical application thus far. Conversely, Toshimasa *et al*. [28] discovered a novel class of inhibitor molecules containing selenium, offering new avenues for drug development. This discovery represents a significant advancement toward the creation of novel therapeutic agents.

Yaoita *et al*. [29] investigated the effectiveness of drugs and TAFI values by inducing experimental thrombosis in rats using a renovascular hypertensive model. They assessed the impact of interventions including antiplatelet, anticoagulant, profibrinolytic, and antioxidative agents. After antihypertensive treatment, they noted a decrease in PAI-1, tissue factor, and TAFI levels. This finding, in line with our study, implies that in the context of the unknown origins of hypertension, TAFI levels may diminish with treatment, indicating a positive response to therapy.

Another study has indicated a notable reduction in blood clot formation in mice deficient in TAFI when subjected to FeCl3-induced vena cava thrombosis, implying a potential role for TAFI in pathology. In this

regard, numerous investigations have thoroughly explored the influence of TAFI levels or variations in the TAFI gene on the progression cardiovascular pathologies [30].

Furthermore, Aso *et al*. [23] found that low-density lipoprotein cholesterol independently affects plasma TAFI levels in 105 cases diagnosed with Type II diabetes mellitus. Additionally, subgroup analysis within this study revealed significantly higher plasma TAFI levels in two specific groups: diabetic patients with hypercholesterolemia, with or without accompanying metabolic syndrome [31].

Based on the studies, it is clear that TAFI may play a significant role in the process of essential hypertension and could impact post-treatment processes. Furthermore, it has been implicated in various diseases such as ulcerative colitis [32], antiphospholipid syndrome [33], chronic thromboembolic pulmonary hypertension [34], gestational diabetes [35], acute pancreatitis [36] and Deep Venous Thrombosis [37]. However, more studies are needed to uncover the specific role and mechanisms of TAFI in these conditions.

Limitations

Several limitations should be mentioned for this study. Initially, the number of study subjects was relatively small, which led to a wide range of TAFI levels. Aside from this TAFI can be an auxiliary parameter in explaining the relationship between hyperlipidemia and PHT, menopausal status which has similar demographic etiopathogenetic, and pathophysiological features. Additionally, since measuring only TAFI antigen levels may not fully represent the enzyme's functional status, the measurement of TAFI activity should also be conducted in future studies.

CONCLUSION

In conclusion, TAFI levels are higher in PHT patients than in normotensive individuals, and this is independent of serum cholesterol levels. Additionally, our study found a significant relationship between BMI and TAFI levels. Higher BMI was associated with increased TAFI levels, suggesting that adiposity may influence TAFI concentration and its role in the fibrinolytic system. The precise role and mechanistic pathways of TAFI in the pathogenesis of PHT should be elucidated in further advanced studies to understand its potential as a therapeutic target or biomarker.

Authors' Contribution

Study Conception: AY, NE; Study Design: AY, NE; Supervision: NE; Funding: AY, KO; Materials: AY, KO; Data Collection and/or Processing: AY; Statistical Analysis and/or Data Interpretation: AY, KO; Literature Review: AY; Manuscript Preparation: AY, KO, NE and Critical Review: NE, AY, KO.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Investigation of the relationship between prolactin and infertility by expression levels of kisspeptin (KISS1), KISS1 receptor, neurokinin (NK), NK receptor genes

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ABSTRACT

Objectives: Prolactin level, which rises in the blood during pregnancy and after birth, plays a role in physiological events such as metabolism and reproduction. Increased blood levels of prolactin lead to various disorders. The most important of these are amenorrhea/galactorrhea and disruption of ovulation. Disruption of ovulation is a serious problem and can lead to infertility problems. Kisspeptin (KISS1) and Neurokinins are involved in the control of ovulation. This study aimed to explain the relationship between Prolactin and infertility with the expression levels of KISS1, KISS1 Receptor (KISS1R), Neurokinin (NK), Neurokinin Receptor (NKR) genes.

Methods: Fourty female Wistar Albino rats, 12-16 weeks old, were used in this study. Three groups were formed, 10 rats were in Group-1 as Control, 10 rats were in Group-2 given Saline, and 20 rats were in Group-3 given Metoclopramide (Metpamid, Sifar Turkey). The raising effect of Metoclopramide on blood Prolactin levels leading to infertility was helpful to clarify the process in comparison with the other two groups not given Metoclopramide.

Results: In Group-3 given Metoclopramide, the blood Prolactin levels were found to be significantly higher compared to Group-1 and Group-2 subjects that were not given this drug. Expression values of KISS1, KISS1R and NK, NKR genes were found to be significantly decreased in Group-3, where the Prolactin level increased, compared to the other two groups ($P<0.001$).

Conclusions: In this study, it has been shown that the expression levels of Neuropeptide genes (KISS1, NK) are suppressed with the direct effect of hyperprolactinemia, thus decreasing the amount and functions of Neuropeptides. In our study it was concluded that the negative effects of prolactin elevation on reproduction may be mediated by neuropeptides.

Keywords: Fertilization, infertility, kisspeptin, neuropeptide, prolactin, reproduction

Infertility has been defined by the World Health Organization as a serious universal problem. It is estimated that approximately 17.5% of reproductive-aged couples worldwide has infertility or subfertility [1]. In most cases of infertility, there are problems in the release of hormones that govern the reproductive system. Hyperpolactinemia has an important place among these problems and this condition is more

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common in women. While its prevalence is 0.4% in the adult population, it can be as high as 9-17% in women with reproductive disorders [2]. These values show the effect of Prolactin on infertility, and high Prolactin exerts its inhibitory effect on the hypothalamus [3]. It is known that there is gonadal dysfunction in the case of hyperpolactinemia. LH (Luteinizing Hormone) peak cannot occur in the anovulatory cycle or ovulation is prevented because the progesterone phase is blocked. Gonadotropin Releasing Hormone (GnRH) dependent LH and Follicle Stimulating Hormone (FSH) releases are triggered by Kisspeptins. This has been demonstrated in mice and rats with mutations of G protein coupled receptor 54 (GPR54). Peripherally administered Metastin (Kisspeptin) increases gonadotropin levels in female and male rats and causes ovulation in prepubertal females [4, 5]. Kisspeptins are members of the RF amide-related proteins family and are important regulators of the GnRH neuroendocrine system [6].They are Neuropeptides that act on GPR54 receptors by deriving from a 145 amino acid precursor protein, which is located in the q32 region of chromosome 1 and is transcribed by the gene called kisspeptin (KISS1) [7, 8]. Kisspeptin neurons play a role as the primary mediator in the feedback control of GnRH release [9, 10]. Another protein found to be associated with the release of GnRH in the hypothalamus is Neurokinin B (NKB). This signal peptide is a member of the Tachykinin family and is involved in intracellular signaling in vertebrates and invertebrates. The most well-known Tachykinins in man are Substance P (SP), Neurokinin A (NKA), and NKB, all of which are commonly synthesized in the central nervous system. NKB and its receptor NK3R, which play a role in the human reproductive axis, are encoded by Tachykinin 3 (TAC3) and Tachykinin 3 receptor (TACR3) genes, respectively. Their mouse homologues are the Tachykinin 2 (TAC2) and Tachykinin 2 receptor (TACR2) genes. These genes are widely expressed in the central nervous system of humans and rodents. The expression of NKB and Kiss1 in the same cells in the arcuate nucleus indicates that they may be closely related. Indeed, studies on mice have shown that NKB agonist increases KISS1 expression and thus affects GnRH and subsequently LH release [10, 11]. It has been stated that KISS1 and NKB may be related to each other, as well as to other hormones that have an effect on GnRH secretion in the living system, especially in the hypothalamus. One of them is Prolactin. Hyperprolactinemia prevents fertilization by inhibiting ovulation with its inhibition effect on GnRH secretion. It was aimed to eliminate the inhibition effect of Prolactin on GnRH with the application of Kisspeptin1 to rats with hyperpolactinemia. Thus, anovulation improved and ovulation occurred with the positive effect of KISS1 on GnRH [12].Considering all this literature information, in this study, we examined the related Neuropeptides we identified and the expression levels of their genes. Hyperprolactinemia reduces the expression levels of KISS1 and Neurokinins, called as Neuropeptides, and their receptors genes, thereby stopping their effects that increase GnRH secretion. Thus, high Prolactin level in the blood reduces the functions of these special Neuropeptides and their receptors, and inhibits the release of GnRH through them. In other words, hyperprolactinemia triggers this metabolic process, makes the related Neuropeptides and their receptors hypoactive, indirectly inhibits the release of GnRH upon this hypoactivation, thus providing infertility.

METHODS

Animal Model

In this study, we created a female animal model that their reproduction abilities were inhibited through the high blood Prolactin level raised with Metoclopramide. Once the Metoclopramide administration was stopped, reproduction was possible in the same female rats again, when the blood Prolactin level returned to normal. This experimental animal model enabled to observe the increase of blood Prolactin in favor of infertility and also its decrease in favor of fertility. This exemplary model provided an important knowledge base for the investigation of all infertility problems, including the disturbed menstrual cycle, in determining the negative side effects of Metoclopramide-containing drugs, which have been applied clinically for various treatments in humans for years.

Three groups of Wistar Albino female rats weighing 200-250 g selected as 12-16 weeks old were used in this study. The number of rats was 40 in total. They were divided into three groups, including 10 for Controlgroup,10 only Saline administered group, and 20 only Metoclopramide (Metpamid, Sifar Turkey) ad-

ministered group, so that we separated them as Group-1-2-3 consecutively, as shown in Table 1. Blood Prolactin levels and expression levels of KISS1, KISS1 receptor (KISS1R), Neurokinin (NK) and Neurokinin receptor (NKR) genes of all these rats were examined. Table 1 summarizes all these three groups of female rats and their applications.

It was determined that fertilization was inhibited when Metoclopramide was given to female rats, and fertilization was reactivated when Metoclopramide was stopped. Thus, Group-3 was given Metoclopramide for two weeks, and then blood Prolactin levels of rats in all groups were measured. The values measured using the Prolactin ELISA immunoassay kit were compared. It was observed that blood Prolactin levels increased significantly in rats in Group-3, and there was no change of blood Prolactin levels in rats Group-1 and Group-2. Meanwhile, rats in Groups-1, Group-2, and 10 randomly selected rats from Group-3 were additionally used in mRNA Expression studies. Vivantis RNA isolation kit (Vivantis Tecnologies Sdn Bhd) was used for RNA isolation. Using the Applied Biosystems High-Capacity cDNA Reverse Transcription kit (Applied Biosystems™), cDNA was obtained from RNAs. In our study, we performed Real-Time (RT) PCR reaction using TaqMan Gene Expression Assay containing FAM stained probe designed for Kiss1, Kiss1 receptor, Neurokinin and Neurokinin receptor genes. Differences between Threshold cycle (Tc) and Crossing points (Cp) values were measured to determine expression levels.

Ethical Permission

The use of experimental animals in this study was allowed and recorded with reference decision number 1 approved in the 8th session of the local ethics academic authority named Cukurova University Medical Faculty Experimental Research and Application Center dated 21August 2013. The animals were carefully treated in accordance with the guidelines confirmed by this official permission.

Statistical Analysis

When summarizing the data, variables are expressed as mean ± standard deviation median (min-max) value. The Kruskal-Wallis Test was used for three or more group comparisons, and then the Mann-Whitney U test was used for pairwise comparisons or direct two group comparisons for expression values. In the evaluations of the variables, differences where $p<0.05$ were considered statistically significant. IBM SPSS Statistics 28.0.1 package program was used in the analysis of the data. Prolactin levels in Group-3 given Metoclopramide were found to be significantly higher than Group-1 and Group-2 who were not given this drug. Expression values of Kiss1, Kiss1 receptor and Neurokinin, Neurokinin receptor genes were found to be significantly decreased in Group-3, where the Prolactin level increased, compared to the other two groups ($P<0.001$). Prolactin levels were measured in these three groups. As a result of the analysis, Prolactin level was the highest in Group-3 given Metoclopramide, Prolactin levels were found to be low in Group-1 and Group-2, which were not given Metoclopramide.

Differences between Threshold Cycle (Ct) and Crossing Points (Cp) values were measured to determine expression levels. The Gene Expression levels of the subjects in the Control group were calculated with the mRNA Gene Expression Assay for comparisons with the other groups.

Table 1. Group of experimental animals (rats)

Groups of rats	Saline application	Metoclopramide application	Expression evaluation	Follow up of pregnancy
Group-1	-	-	+	+
Group-2	+	-	+	+
Group-3	-	+	+/-*	+/-*

*10 randomly selected female rats from Group-3 were combined with male rats for fertilization after the experimental applications related to all these groups.

The differences between the rats in Group-3 given Metoclopramide and the other groups were found to be statistically significant ($P<0.001$), as shown in Table 2.

RESULTS

It was determined that fertilization was inhibited when Metoclopramide was given to female rats, and fertilization was reactivated when Metoclopramide was stopped. Thus, Group-3 was given Metoclopramide for two weeks, and then blood Prolactin levels of rats in all groups were measured.

Prolactin levels were measured in three groups. As a result of the analysis, Prolactin level was the highest in Group-3 given Metoclopramide, Prolactin levels were found to below in Group-1and Group-2, which were not given Metoclopramide (Table 2).

Expression values of KISS1, KISS1R and NK genes were found to be significantly decreased in Group-3, where the Prolactin level increased, compared to the other two groups (P<0.001) (Figs.1, 2, and 3).

No statistically significant difference was found in Group 3 in terms of NKR expression value (P=0.052) (Fig. 4).

Following the experimental applications,10 randomly selected female rats from Group-3 were brought together with male rats and their pregnancy status was examined. It was determined that 8 of the rats became pregnant after 3 months, and 2 of them became pregnant after 4 months.

DISCUSSION

Infertility is defined as the inability to achieve pregnancy within 12 months despite regular vaginal sexual intercourse with the same partner without using any contraceptive method [1]. Infertility can be caused by various reasons. Prolactin is one of the hormones associated with infertility. The idea that high blood Prolactin levels can lead to infertility by decreasing GnRH secretion is an important fieldof research [13]. In studies conducted to show the relationship between Prolactin and infertility, blood Prolactin levels of the subjects were increased and fertilization decreased [12]. It is noteworthy that in another study, all transgenic female mice unable to synthesize Prolactin were found to be infertile [14]. In this case, if the level of Prolactin in the blood is zero, it is an important issue that should be investigated further. This may be a different metabolic process to compensate for the absence of Prolactin and perhaps gains more activity than necessary, which can also cause infertility. By the way, Ormandy *et al* detected many reproductive disorders such as disruption of the menstrual cycle and decreased fertilization in transgenic mice with mutated Prolactin receptor gene [15]. In our study, blood Prolactin levels of the Metoclopramide group were found to be significantly higher than the Control group and the Saline group. Owing to our experimental animal model, we succeeded to realize Prolactin elevation as endogenous and reversible. In this way, we observed that female rats given Metoclopramide did not become pregnant, but pregnancy occurred in the same rats after the effect of Metoclopramide was over. We noticed that pregnancies were absolutely normal in female rats in Group-1 and Group-2, which were not given Metoclopramide. All 10 randomly selected female rats from Group-3 gave birth 3 months after Metoclopramide administration was stopped. This development, which

Table 2. Distribution of prolactin levels and comparisons between the groups of rats

Groups of rats	Prolactin levels (ng/mL)	P value (multiple comparisons)
Group-1 (Control)	23.0±5.4 20.9(18.5-35.7)	**-**
Group-2 (Saline)	29.7±10.0 28.5(19.7-55.9)	**0.364***
Group-3 (Metoclopramide)	53.3±14.3 53.0(34.0-73.4)	**<0.001*** **0.017****
P value	**<0.001**	

Data are shown as mean±standard deviation and median (minimum-maximum) *Comparison with Control, **Comparison of the other two groups

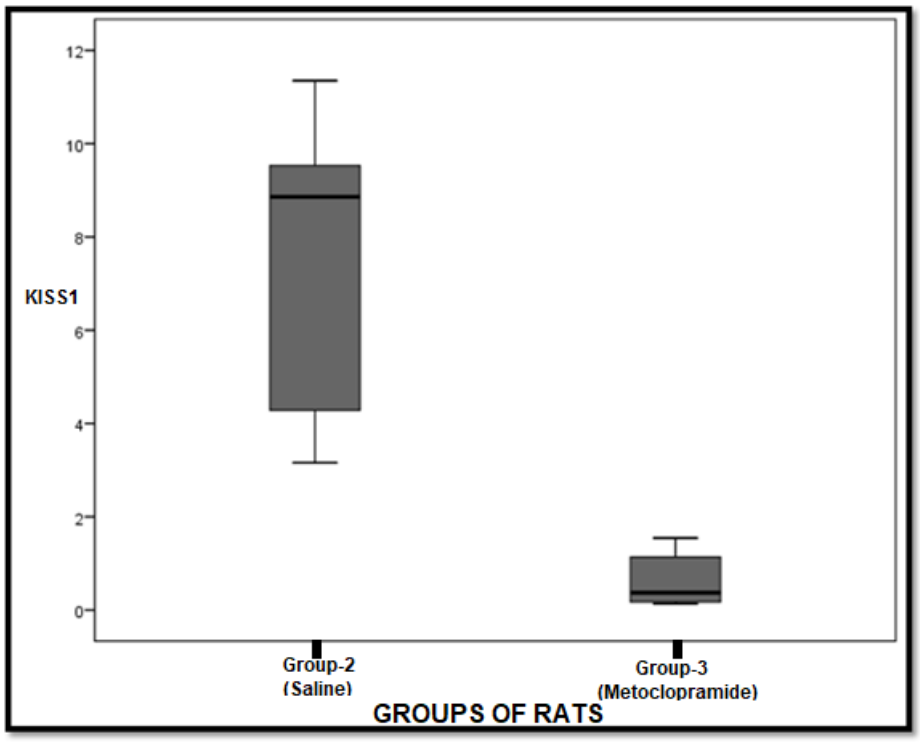

Fig. 1. Expression levels of KISS1 in saline and metoclopramide Groups. The difference in expression levels of KISS1 between Group-2 (Saline) and Group-3 (Metoclopramide) was statistically significant (P<0.001).

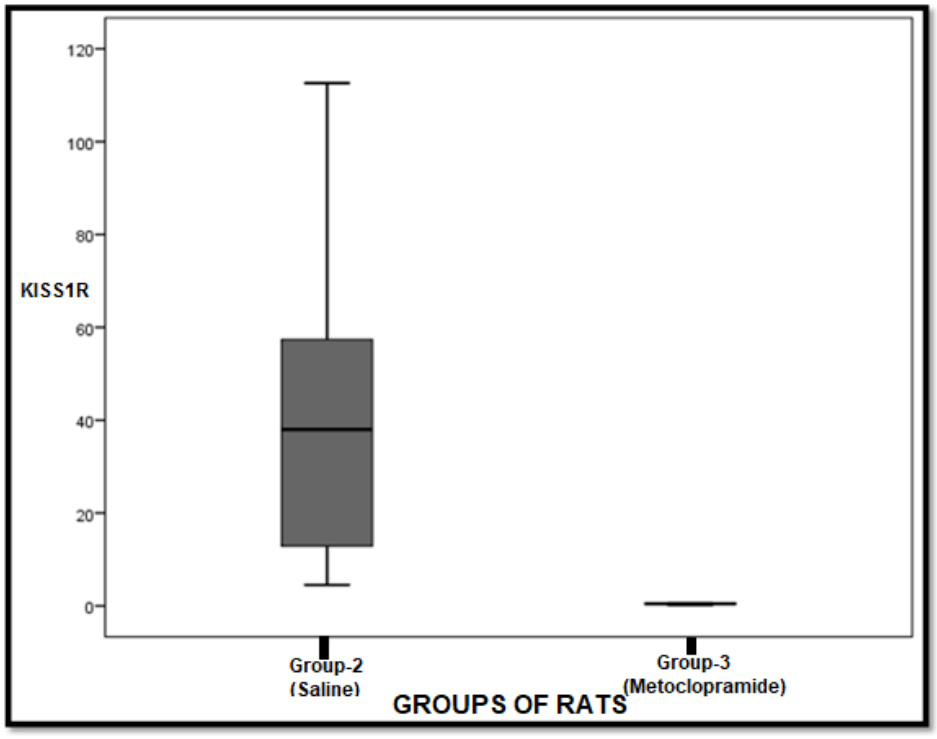

Fig. 2. Expression levels of KISS1R in saline and metoclopramide groups. The difference in expression levels of KISS1R between Group-2 (saline) and Group-3 (metoclopramide) was statistically significant (P<0.001).).

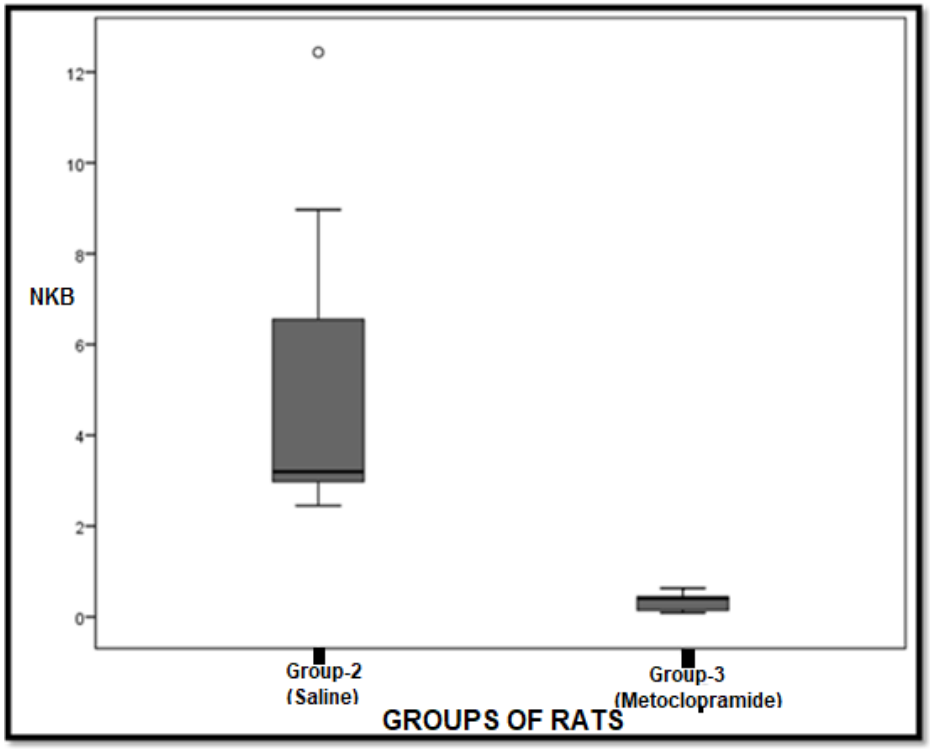

Fig. 3. Expression levels of NKB in saline and metoclopramide Groups. The difference in expression levels of NKB between Group-2 (saline) and Group-3 (metoclopramide) was statistically significant (P<0.001).

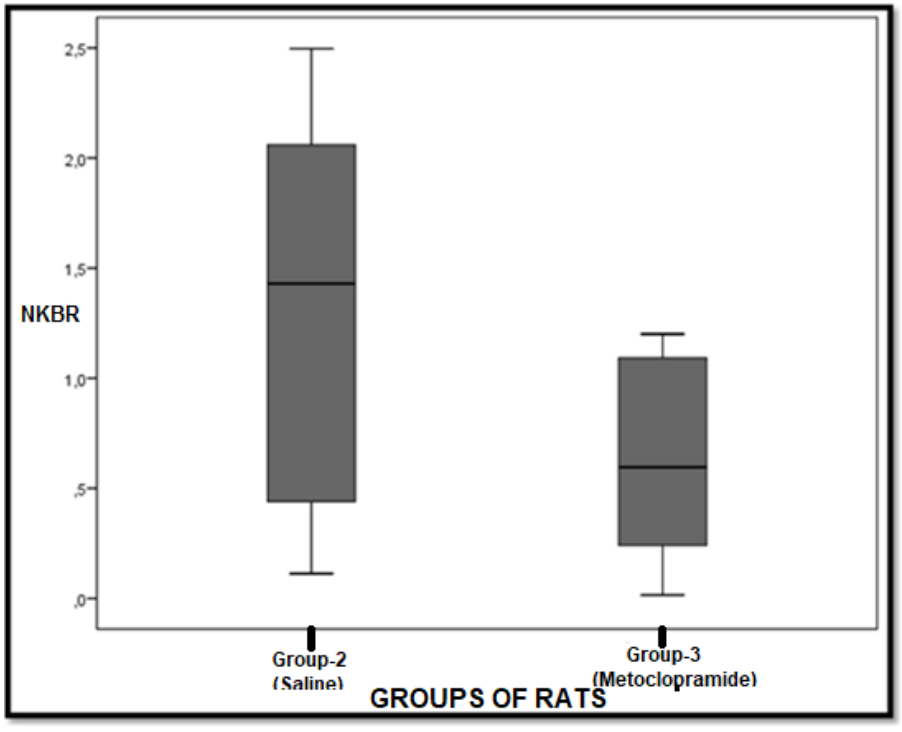

Fig. 4. Expression levels of NKBR in saline and metoclopramide groups. The difference in expression levels of NKBR between Group-2 (saline) andGroup-3 (metoclopramide) was considered tobe borderline significant (P=0.052).

resulted in fertilization and delivery, confirms our opinion about the effect of Metoclopramide, which triggers infertility by elevating the Prolactin level in the blood. If the effect of Metoclopramide is over, the inhibiting pressure of Prolactin on ovulation will be diminished, because Prolactin blood level will decrease to normal gradually after stopping the experimental Metoclopramide administration. Bachelot and Binart suggested that Prolactin causes anovulation by inhibiting the release of GnRH and thus decreasing the amount of LH and FSH in the blood. However, they did not elucidate how Prolactin does this inhibition and the existence of Neuropeptides that mediate it [16].The results of our study enabled use to set an example that can lead to new research on this subject. Meanwhile, several other studies have provided new evidence that Prolactin may modulate the reproductive axis by acting on a specific population of hypothalamic neurons expressing the KISS1gene [17,18].

Loss-of-function mutations in genes encoding Kisspeptins or in the KISS1R cause puberty problems and infertility by negatively affecting the reproductive system in humans and animal models [19]. In the study of Topaloğlu *et al*. [20], it was shown that hypogonadotropic hypogonadism developed in all subjects with KISS1 mutation. In another study, the suppressive effect on GnRH caused by high blood Prolactin levels was abolished with KISS1 injection, thereby returning the ovulation process to normal. The fact that ovulation occurs again by daily injections of KISS1 to female mice that become infertile with Prolactin infusion confirms our comments [12]. In our study, we showed that elevated Prolactin decreased KISS1 and KISS1R expressions in female rats by comparing with our Control and Saline groups. KISS1, which has proven to play an important role in increasing GnRH secretion, is not the only Neuropeptide to undertake this task. Studies conducted in recent years have shown that NKB also has effects that increase the release of GnRH [21]. The neuroanatomical relationship between Kisspeptins and NKB and the demonstration that both are effective in GnRH stimulation and gonadotropin release suggest that these two Neuropeptides may mediate the effects of each other on puberty and fertility [22]. The data we obtained in our study also supports this thesis. Expression of NBP was significantly decreased in Metoclopramide administered subjects compared to Control and Saline groups.

CONCLUSION

This study revealed that KISS1, KISS1R, NK and NKR mRNA expressions were significantly decreased in our subjects whose blood Prolactin levels were elevated by using Metoclopramide for comparison to the Control and Saline groups. All data are compatible with the literature and give an accurate idea to explain the inhibitory effect of Prolactin on the HPG axis. In light of these results, many kinds of pharmacological agents can be checked out, if they have any effect of raising blood Prolactin levels so that their biological effects can lead to this specific clinical outcome of infertility. As a matter of fact, the present literature in this field is not enough to fully understand the whole cycle. For this reason, GnRH neuron activities, histopathological evaluation of the hypothalamic region, receptor functions in the uterus, and many more factors should also be examined in detail.

Authors' Contribution

Study Conception: EA; Study Design: MBY, EA; Supervision: MBY, EA; Funding: EA; Materials: EA; Data Collection and/or Processing: EA; Statistical Analysis and/or Data Interpretation: EA, MBY; Literature Review: EA; Manuscript Preparation: EAand Critical Review: EA.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Is prostate-specific antigen density superior than prostate-specific antigen kinetics and prostate volume in predicting clinically insignificant prostate cancer?

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ABSTRACT

Objectives: In this study, we aimed to evaluate the parameters that could predict clinically insignificant prostate cancer (ciPCa) in men who underwent transrectal ultrasound (TRUS)-guided prostate biopsy.

Methods: Data of patients who underwent transrectal prostate biopsy between January 2015 and November 2019 were examined retrospectively. Free/total PSA ratio (fPSA%), serum total and free prostate-specific antigen (PSA) levels, prostate volumes (PV) measured by ultrasonography, and PSA density (PSAD) values of the patients before biopsy were recorded. ciPCa patients were defined as patients with Gleason scores ≤6 and clinical stage ≤T2a (Group 1). The remaining patients (Gleason score >6 and clinical stage >T2a) were included in Group 2 (clinical significant prostate cancer (csPCa). The parameters examined before biopsy were compared between groups.

Results: After performing the exclusion criteria, the study counts in 168 patients with the current data of total/free PSA levels, age, PV calculated by TRUS, rectal examination findings, and pathology reports. Group 1 consisted of 115 patients and Group 2 consisted of 53 patients. In the univariate analysis, PV, total PSA and PSAD were found significantly different between groups, while age, free PSA, and fPSA% showed no significant difference between the two groups. According to the results of the multivariate analysis, the independent predictor of ciPCa was determined to be PSAD while total PSA and PV were not independent predictors.

Conclusion: PSAD was found to be superior to other PSA kinetics in predicting ciPCa.

Keywords: Prostate-specific antigen, prostate cancer, prostate-specific antigen density, prostate volume

Prostate cancer (PCa) is the most commonly diagnosed cancer in men after lung cancer and is a leading cause of cancer-related deaths. In 2020, 1.4 million people were diagnosed, accounting for 15% of all cancers [1]. Prostate-specific antigen (PSA) screening test is widely used all over the world for early diagnosis of the disease. However, PSA causes difficulties in the diagnosis of prostate cancer. Because the specificity of PSA is low. Therefore, various studies have been conducted to get better cancer prediction using different PSA kinetics such as age-referenced PSA, Free/total PSA ratio (fPSA%), PSA density (PSAD), and PSA velocity [2-4]. In most studies, these diagnostic methods have been used to pre-

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dict prostate cancer patients. Their effectiveness in distinguishing clinically significant cancers has been less studied. However, in the diagnosis of PCa, the main goal is to distinguish between clinically significant prostate cancer (csPCa) and clinically insignificant prostate cancer (ciPCa) to reduce overdiagnosis. On the other hand, adenocarcinoma must be seen in prostate biopsy samples for a definitive diagnosis, but the cancer is detected in only 25% of all biopsies [5]. In addition, various complications ranging from simple hematuria to sepsis may occur as a result of prostate biopsy [6].

Therefore, in this study, we aimed to investigate the success of PSA kinetics and PV in forecasting ciPCa in order to decrease redundant biopsies and overdiagnosis. In addition, we aimed to determine the proper cut-off values of the parameters that would be statistically significant in predicting ciPCa. The primary outcome of the study is to investigate the role of PSA kinetics in predicting ciPCa patients, and the secondary outcome is to determine the cut-off values of these parameters in predicting ciPCa.

METHODS

For the study, ethics committee approval was obtained from the University of Health Sciences Bursa Yuksek Ihtisas Training and Research Hospital ethics committee, dated 29.01.2020 and numbered 2020/01-08. The data of 1901 men who underwent transrectal ultrasonography-guided prostate biopsy patients between 40-80 years in a urology outpatient clinic between February 2015 and November 2019 were retrospectively scanned. Indications for prostate biopsy was serum PSA levels >2.5 ng/mL and abnormal digital rectal examination (DRE). Patients with PSA levels >10 ng/mL, patients receiving 5-alpha-reductase inhibitor therapy, and patients with a history of any invasive treatment for benign prostatic obstruction were excluded from the study. Additionally, patients who had undergone an endoscopic procedure, biopsy, urinary tract infection, and urinary retention within the last month were also excluded from the study.

Serum PSA levels were obtained in ng/mL using chemiluminescent microparticle immunoassay (CMIA) before any prostate manipulation. fPSA% was calculated by free PSA/total PSA×100. The patients' PV was calculated by measuring three dimensions of the prostate (PV = length×width×length×0.52). PSAD was obtained by dividing the serum total PSA level by the prostate volume measured by ultrasonography. The patients included in the study are those who have had at least 12 core biopsies. Patients who underwent multiple biopsies were included in the study according to their last biopsy results, PSA levels, and prostate volumes from the last biopsy period.

Clinically insignificant prostate cancer (low-risk patients) was defined as Gleason score ≤6 and clinical stage ≤T2a. Patients who met both ciPCa criteria were included in Group 1, and the remaining prostate cancer patients were included in Group 2. Between groups, PSAD and prostate volume, age, total PSA, and free PSA were compared.

Statistical Analysis

Statistical analysis was performed using SPSS version 15.0 software (SPSS, Inc., Chicago, IL, USA). Shapiro-Wilk test was used to interpret the suitability of the data to the normal distribution curve. Continuous and categorical data were compared using the Mann-Whitney U test and Chi-square test, respectively. Logistic regression multivariate analysis was performed to identify independent predictive factors. The receiver operating characteristic (ROC) curve was used to evaluate and compare the effectiveness of PSAD, prostate volume, and total PSA. $P<0.05$ value was considered statistically significant.

RESULTS

A total of 168 patients with available data were included in the study. ciPCa consisted of 115 patients and csPCa consisted of 53 patients. Table 1 includes the baseline data of the groups and the comparison of the groups in terms of these parameters.

In univariate analysis, PV was found to be significantly higher and total PSA and PSAD were significantly lower in Group 1 compared to Group 2. Age, free PSA, and fPSA% did not differ significantly between the two groups (Table 1). In ROC analysis, the sequence of AUCs was determined as total PSAD>PV> total PSA (Table 2).

Table 1. Clinical characteristics of the patients

Parameters	Total Cohort (n=168)	Group 1 (n=115)	Group 2 (n=53)	Group 1 vs. Group 2 P value
Age (years)				
Mean±SD	64±7.19	64.59±7.06	65.81±7.22	0.168
Median (min-max)	65 (44-81)	65 (44-81)	66 (48-79)	
Total PSA (ng/mL)				
Mean±SD	6.35±1.96	6.08±1.96	7.09±1.68	**0.004**
Median (min-max)	6.32 (1.28-9.89)	5.97 (1.28-9.89)	7.19 (3.90-9.86)	
Free PSA (ng/mL)				
Mean±SD	0.34±0.82	1.26±0.63	1.52±1.11	0.222
Median (min-max)	1.23 (0.19-6.70)	1.17 (0.19-3.32)	1.27 (0.36-6.70)	
Free/Total PSA				
Mean±SD	0.21±0.11	0.21±0.09	0.22±0.14	0.688
Median (min-max)	0.19 (0.05-0.89)	0.18 (0.05-0.53)	0.19 (0.05-0.84)	
Prostate volume (cc)				
Mean±SD	50.32±29.77	63.31±28.23	44.31±32.68	**0.003**
Median (min-max)	44 (10-206)	46 (15-206)	33 (10-190)	
PSAD (ng/mL/cc)				
Mean±SD	0.166±0.103	0.14±0.08	0.22±0.12	**<0.001**
Median (min-max)	0.13 (0.02-0.63)	0.11 (0.02-0.44)	0.20 (0.02-0.63)	

PSAD=Prostate-specific antigen density, PSA= Prostate-specific antigen, SD=standard deviation, min=minimum, max=maximum, Group 1=clinically insignificant prostate cancer, Group 2= clinically significant prostate cancer

Multivariate analysis was applied to PSAD, PV, and total PSA, which were found to be significant in univariate analysis. According to the multivariate analysis results, the independent predictor of ciPCa was determined to be PSAD, while total PSA and PV were not independent predictors (Table 3). Cutoff values for PSAD, total PSA, and PV were determined for the prediction of ciPCa. ROC analysis revealed a cut-off value of 0.157 ng/mL/cc with 69.8% sensitivity and 69.6% specificity for PSAD, and 6.31 ng/mL with 64.2% sensitivity and 55 specificity for total PSA % and the cut-off value for PV is 35.5 cc, with a sensitivity of 77.2% and a specificity of 55% (Fig. 1). The numbers and percentages of groups, and the p values when patients are divided according to these cut-off values, are shown in Table 4. The distribution of Group 1 patients into quartiles when grouped by PSAD, total PSA, and PV is shown in Table 5.

Table 2. The AUCs for total PSA, prostate volume, and PSAD in predicting clinically significant prostate cancer.

	AUC	%95 CI	P value
Total PSA	0.639	0.552-0.725	**0.004**
Prostate volume	0.641	0.547-0.734	**0.003**
PSAD	0.713	0.625-0.801	**<0.001**

PSAD=Prostate-specific antigen density, PSA= Prostate-specific antigen, AUC=Area under the curve

Table 3. Multivariate analysis of independent predictors of clinically significant prostate cancer.

	Odds ratio	95% Confient interval	P value
Total PSA	1.044	0.834-1.307	0.708
Prostate volume	1.015	0.998-1.032	0.094
PSAD	50.792	103.4-24930132.4	**0.001**

PSAD=Prostate-specific antigen density, PSA= Prostate-specific antigen

DISCUSSION

Since PSA is insufficient to predict prostate cancer, both new laboratory and new imaging methods are being developed to predict ciPCa [7, 8]. These methods aim to reduce overdiagnosis and subsequent overtreatment. The desired features of these methods are that they are cheap, easily accessible, and non-invasive. In our study, we investigated whether PSAD, prostate volume, total PSA, and fPSA%, which can be measured in peripheral blood and measured on USG, have a place in the prediction of ciPCa. According to our study results, we concluded that among PSA derivatives, only PSAD can predict ciPCa.

The search for more specific and sensitive markers continues to predict ciPCa in the patient group with PSA values in 4-10 ng/mL. Since it is known that the PSA level increases as the prostate volume increases, Benson *et al*. in their article published in 1992, they wrote that the ratio of serum PSA level to prostate volume could facilitate the detection of PCa. In this study, where it was first described, PCa and BPH patients

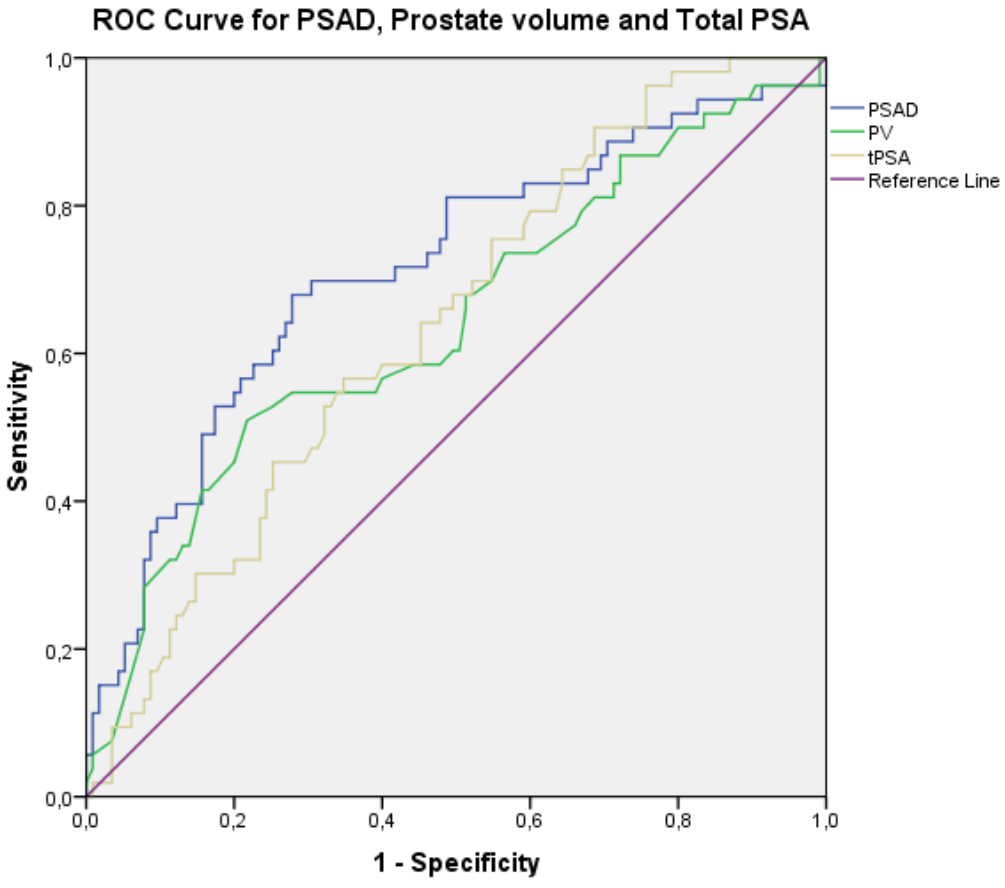

Fig. 1. ROC analysis for PSAD, total PSA and PV for the prediction of ciPCa. PSAD=Prostate-specific antigen density, PSA= Prostate-specific antigen, PV= Prostate volume, ciPCa= clinically insignificant prostate cancer.

Tablo 4. Comparison of patient's age, total PSA, free PSA, free/total PSA ratio, prostate volume, and clinically significant PCa according to the cut-off value of PSAD.

Parameters	PSAD		P value
	<0.157	>0.157	
Number of pateints			
(n=168)	95	73	
(100%)	(%56.5)	(%43.5)	
Age (years)			0.953
Mean±SD	65.15±6.37	64.75±8.01	
Median (min-max)	65 (47-78)	66 (44-81)	
Total PSA (ng/mL)			
Mean±SD	5.72±1.86	7.25±1.66	**<0.001**
Median (min-max)	5.80 (1.28-9.89)	7.52 (3.78-9.86)	
Free PSA (ng/mL)			
Mean±SD	1.34±0.66	1.35±1.01	0.315
Median (min-max)	1.28 (0.19-3.22)	1.07 (0.36-6.70)	
Free/Total PSA			
Mean±SD	0.23±0.09	0.19±0.12	**<0.001**
Median (min-max)	0.22 (0.07-0.56)	0.16 (0.05-0.84)	
PV (cc)			
Mean±SD	65.73±31.02	30.59±10.49	**<0.001**
Median (min-max)	60 (24-206)	31 (10-58)	
Group			
Group 1 (ciPCa)	79 (%83.1)	36 (%49.3)	**<0.001**
Group 2 (csPCa)	16 (%16.9)	37 (%50.7)	

PSAD=Prostate-specific antigen density, PSA= Prostate-specific antigen, PV=Prostate volume, PCa=Prostate Cancer, csPCa=clinically significant prostate cancer, ciPCa=clinically insignificant prostate cancer, SD=standard deviation, min=minimum, max=maximum

were compared and a statistically significant higher rate was found in the PCa group [9]. PSAD is obtained by dividing the PSA value by the prostate volume [1]. As this rate increases, the probability of having csPCa increases.

Many studies in the literature have shown a relationship between PSAD and PCa. In the study of Yusim *et al*. [10], 992 patients were included. They showed that PSAD had a role in predicting both PCa and csPCa. They concluded that patients with PSAD value below 0.09 ng/mL were less likely to have csPCa [10]. Omri *et al*. [11] included 364 patients to the study and, they divided the patients into 3 groups according to their prostate volume (<50 cc, 50-75 cc, >75 cc). According to the results, PSAD was correlated with csPCa in medium and low-sized prostates, but not in large-sized prostates [11]. Nordstrom *et al*. [12] in their study including 5291 patients, found the PSAD cut-off value to be lower than similar studies (<0.07 ng/mL/cc). According to the authors, not performing a prostate biopsy in men with PSAD ≤0.07 ng/mL/cc would prevent 19.7% of patients from biopsy, while 6.9% of patients with csPCa would be missed [12]. Kosaka *et al*. [13] in their study, the PSAD cut-off value in predicting csPCa was found to be 0.032 ng/mL/cc. This cut-off value is slightly higher than the known value. The reason for this was thought to be that the study group of Kosaka *et al*.

Table 5. The distribution of Group 1 patients in quartiles when stratified by PSAD, total PSA, and PV

Parameter		<cut-off n (%)	>cut-off n (%)	P value
PSAD cut-off=0.157 ng/mL/cc	Total	95 (%56.5)	73 (%43.5)	**<0.001**
	Group 1	79 (%83.1)	36 (%49.3)	
	Group 2	16 (%16.9)	37 (%50.7)	
Total PSA cut-off=6.31 ng/mL	Total	82 (%48.8)	86 (%51.2)	**0.023**
	Group 1	63 (%76.8)	52 (%60.4)	
	Group 2	19 (%23.2)	34 (%29.6)	
Prostate Volume cut-off=35.5 cc	Total	61 (%36.3)	107 (%63.7)	**<0.001**
	Group 1	32 (%52.4)	83 (%77.5)	
	Group 2	29 (%47.6)	24 (%22.5)	

PSAD=Prostate-specific antigen density, PSA= Prostate-specific antigen, PV=Prostate volume, Group 1=clinically insignificant prostate cancer, Group 2= clinically significant prostate cancer

[13] consisted of patients under the age of 50. Although there is heterogeneity in the cut-off value of the studies, the cut-off value specified in the European Association of Urology guidelines is 0.1-0.15 ng/mL/cc [1]. In our study, the PSAD cut-off value was determined as 0.157 ng/mL/cc, in line with the guideline.

To overcome different cut-off values in PSAD, measuring prostate size by MRI can provide standardization. In the study performed by Distler *et al*. [14], it was stated that when MRI and PSAD were combined, the negative predictive value for csPCa increased from 79% to 89%.

The free/total PSA ratio is also an important PCa predictor. According to biopsy pathology results in men with serum PSA values in the range of 4-10 ng/mL, csPCa is detected in more than half of men with fPSA % <0.10. Gao *et al*. [15] evaluated 528 prostate cancer and 1127 BPH patients in their study and they determined a wider gray zone (2.5-25 ng/mL), contrary to what is known. According to the results, fPSA% was found to be the most effective predictor in patients with PSA values in this range, with an AUC value of 0.700 (cut-off value: 15.5%). [15]. In the study conducted by Shore *et al*. [16], the predictive effects of pro-PSA, total PSA, the prostate health index, and free PSA% were compared for PCa. fPSA% was found to be effective both in distinguishing PCa-BPH and in distinguishing between aggressive and non-aggressive PCa. However, the prostate health index was found to be superior to fPSA% in distinguishing between PCa and BPH. [16]. In this study, unlike the above studies, there was no statistically significant difference in fPSA% between the two groups.

The prostate volume provides important information for predicting malignant prostate diseases. However, data on its use in csPCa are limited. Erdogan *et al*. [17] found that the prostate volume in the patient groups with PSA levels of 2.5-10 ng/mL and 10-30 ng/mL was statistically significantly higher in the BPH group than in the PCa group. Chen *et al*. [18] stated in their study that lower rates of prostate cancer were detected in the patient group with larger prostate volume. Huang *et al*. [19] in their study investigated whether prostate volume has an additional predictive contribution to the prostate health index in the prediction of PCa. According to the results, they stated that prostate volume had no additional predictive value [19]. In the study we present, prostate volume was

found to be statistically significantly lower in the clinically significant prostate cancer group but was not found to be a predictive factor in multivariate analysis.

Limitations

First of the limitations of the study is that it was conducted with a small number of patients and a retrospective method. Another limitation is operator-induced differences in prostate volume measurement that may affect the PSAD value.

CONCLUSION

According to our results, PSAD plays an important role in predicting ciPCa. When deciding on biopsy, especially in patients with PSAD < 0.157 ng/mL/cc, benefiting from additional predictive factors will be beneficial to avoid overtreatment.

Ethical statement

This research was approved the University of Health Sciences Bursa Yuksek Ihtisas Training and Research Hospital ethics committee, dated 29.01.2020 and numbered 2020/01-08.

Authors' Contribution

Study Conception: SA, ÖE; Study Design: VÇ, AE; Supervision: EÖ, RÖ; Funding: UA, SÖ; Materials: SA, ÖE; Data Collection and/or Processing: VÇ, AE; Statistical Analysis and/or Data Interpretation: EÖ, RÖ; Literature Review: UA, SÖ; Manuscript Preparation: SA and Critical Review: SÖ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Effect of transdermally applied nitroglycerin or lidocaine before transradial coronary angiography on procedure success and complications

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ABSTRACT

Objectives: We investigated the effect of transdermal nitroglycerin or lidocaine application on puncture time, number, and complications in patients who underwent transradial coronary angiography.

Methods: Patients with topical saline applied to the radial artery before the procedure were designated as Group 1 (n=59), those with topical nitrate were designated as Group 2 (n=43), and those with topical lidocaine were designated as Group 3 (n=40). The groups' puncture time, number, and complication rates were compared.

Results: While our average puncture time was 142±122 seconds in all patients, this time was measured as 171±131 seconds in Group 1, 88±48 seconds in Group 2, and 157±146 seconds in Group 3 (P=0.021). During the procedure, radial artery spasm was observed in 15.2% of patients in Group 1, 6.9% in Group 2, and 12.5% in Group 3 (P=0.043). Radial artery occlusion was seen in 8% of patients in Group 1, and 2.5% in Group 3, while it was not observed at all in the nitrate-applied group (P=0.041).

Conclusion: The topical application of nitroglycerin before transradial angiography is a feasible strategy to reduce radial puncture time and number, facilitate trans-radial catheterization, and decrease the incidence of radial artery spasm and occlusion.

Keywords: Transradial coronary angiography, transdermal, nitroglycerin, lidocaine, spasm

New guidelines for myocardial revascularization recommend trans-radial access as the standard approach unless there are procedural drawbacks [1, 2]. For diagnostic angiography and percutaneous coronary procedure (PCI) in coronary artery disease, the transradial approach (TRA) is associated with less bleeding, access site complications, lower mortality, and higher patient comfort compared to the TFA [3].

Due to the smaller vessel size in the trans-radial approach, some interventions are technically difficult. The possibility of vascular spasm may be considered among its disadvantages [4]. It is reported in the literature that the incidence of radial artery spasm is between 6.8% and 30% [5]. The spasm occurs due to decreased nitric oxide release and increased catecholamine release due to mechanical stimulation and endothelial damage during catheter manipulations. We investigated the effect of transdermal nitroglycerin or lidocaine application on puncture time, number, and complications in patients who underwent transradial angiography.

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METHODS

Study Population

Our study included patients who were examined at the Cardiology outpatient clinic between February 2023 and August 2023 with an indication for angiography. Patients with acute coronary syndromes, severe heart failure, hemodynamic instability, uncontrolled hypertension or diabetes, previous radial access site insufficiency, sensitivity to lidocaine or nitrate, and those with a history of coronary artery bypass surgery were excluded from the study.

Patients were randomly assigned to three groups: topical nitrate, topical lidocaine, and placebo. Medical histories of all patients included in the study were recorded.

Before the procedure, electrocardiography was performed, and blood pressure and pulse rates were noted. Group assignments were documented on a separate data sheet and were not disclosed to the doctors performing the procedure or to the patients. To prevent selection bias in patients undergoing coronary angiography, randomization was conducted by a third party unaware of the patient's clinical information.

The study was approved by the Tekirdağ Namık Kemal University Non-invasive Clinical Research Ethics Committee (Decision date: 28.02.2023 and No: 2023.36.02.14).

Topical Cream Application

Patients were administered topical lidocaine or topical nitrate at least 30 minutes before the procedure on their right wrists. In sequence, 40 mg of lidocaine cream was applied to the topical lidocaine group, 30 mg of nitroglycerin (NTG) ointment (Fougera NY) was applied to the topical nitrate group, and a topical lotion (selected to resemble the appearance of active creams) was applied to the placebo group in the radial artery region. Vital signs were recorded initially, 15 minutes after the procedure, and every 30 minutes before the procedure.

Radial Puncture

Three minutes before radial artery puncture, local subcutaneous anesthesia was applied with a 1 mL injection of 1% lidocaine. Radial artery puncture was performed by an experienced cardiologist using a 20-gauge needle and standard techniques. The working doctor initiated the puncture duration at the beginning of the procedure using a stopwatch. The puncture duration was defined as the time from the needle touching the forearm at the start of the puncture to the complete insertion of the sheath.

All procedures were performed using 6F radial sheaths. To assess forearm pain, a verbal pain scale was utilized by a catheter laboratory nurse. The nurse, unaware of the patient's group assignment, queried and reported it. All patients received intra-arterial spasmolytic treatment with heparin and 200 µg nitroglycerin.

Procedure time, puncture time (Time from subcutaneous lidocaine infiltration to puncture), number of puncture attempts, and all complications were recorded. Pre-discharge examinations were conducted, and any developed complications were noted. Before discharge, patients were examined by the doctor for local complications and clinically assessed. Blood pressure and pulse measurements were taken and recorded. One week after discharge, patients were called for a follow-up, examinations were repeated, and procedure-related complications were noted. The primary objective of this study was to evaluate the effect of topical lidocaine or nitrate application on puncture duration and frequency. The secondary objectives were to investigate the effect on pain during puncture and evaluate its impact on complications during discharge and at 1-week follow-up examinations.

Statistical Analysis

Descriptive statistics for baseline parameters of continuous variables with normal distribution were presented as mean ± standard deviation, while those without normal distribution were presented as median (minimum-maximum). Qualitative variables were presented as numbers and percentages. The significance of differences in means of continuous variables was evaluated using the Student's t-test when the number of independent groups was two and the ANOVA test when the number of groups was three. To compare the group medians of continuous variables that did not adhere to the normal distribution, the Mann-Whitney U test was employed for the presence of two independent groups, and the Kruskal-Wallis test was used for the presence of three independent groups. If the Kruskal Wallis test statistics indicate significance, post-hoc Tukey or non-parametric multiple comparison tests were utilized to identify the conditions causing the dif-

ference. P-value below 0.05 was considered statistically significant. All tests were performed using the SPSS 22.0 (SPSS Inc., Chicago, IL) software version.

RESULTS

Patients participating in our study were divided into three groups: group 1, the control group (n=59), group 2, with nitrate-containing cream applied (n=43), and group 3, with lidocaine-containing cream (n=40) (Table 1). Successful puncture was achieved in 85 patients (59.9%) on the first attempt, while 57 patients (40.1%) required 2 or more punctures. TRA was successfully performed in 131 patients (92.3%), while in 11 patients (7.7%), the procedure was continued via the femoral artery due to puncture failure or spasm. The average number of punctures for all patients undergoing TRA during the study was 1.7±1. 1, and the average radial puncture duration was 142.2±122 seconds (Table 2). The most frequently observed complication was spasm during the procedure (12%), followed by hematoma in 12 patients (8. 5%) during follow-up after the procedure. During outpatient clinic controls, the arterial ultrasound revealed occlusion in the radial artery in 6 patients (4.2%). No pseudoaneurysm, radial artery dissection, or rupture was observed in any patient throughout the study. Puncture time was significantly lower in Group 2. (Group 1; 171±131 seconds, Group 2; 88±48 seconds and Group 3; 157±146 seconds) (P=0.002) (Table 2).

When comparing the three groups based on the number of punctures, a significant difference was observed (P<0.018). This difference was found to be between the group with nitrate application (Group 2) and the group without cream application (Group 1) (P=0.014), while no significant difference was observed between the lidocaine group (Group 3) and the

Table 1. Demographic data for each group

Variable	Group 1 (Control) (n=59)	Group 2 (Nitrate) (n=43)	Group 3 (Lidocaine) (n=40)	P value
Male, n (%)	32 (54. 2)	29 (67. 4)	26 (65)	0.132
Age (years)	61±10	59±12	61±11	0.422
BMI $_{kg/m^2}$	31.87±6.2	28.47±4.7	27.97±4.9	**0.001**
Smoking, n (%)	22 (37.3)	19 (44.1)	11 (27.5)	0.081
Alcohol, n (%)	13 (22)	8 (18.6)	5 (12.5)	0.093
HT, n (%)	38 (64.4)	29 (67.4)	25 (62.5)	0.101
DM, n (%)	20 (33.8)	11 (25.5)	17 (42.5)	0.232
CAD, n (%)	17 (28.9)	12 (27.9)	12 (30)	0.979
HL, n (%)	22 (37.2)	16 (37.2)	16 (40)	0.652
Medication, n (%)				
Antiplatelet	31 (52.5)	21 (48.8)	23 (57.5)	0.322
OAC	5 (8.4)	3 (6.9)	5 (12.5)	0.231
BB	23 (38.9)	15 (34.8)	23 (57.5)	0.546
CCB	7 (11.8)	7 (16.2)	2 (5)	0.433
Statin	20 (33.8)	13 (30.2)	16(40)	0.578
ECG, n (%)				
Sinus	52 (88.1)	41 (95.3)	35 (87.5)	0.492
AF	7 (11.9)	2 (4.7)	5 (12.5)	

Data are shown as mean±standard deviation or n (%). HT=Hypertension, DM=Diabetes Mellitus, CAD=Coronary Artery Disease, HL=Hyperlipidemia, OAC=Oral Anticoagulant, BB=Beta-blocker, CCB=Calcium Channel Blocker, ECG=Electrocardiography, AF=Atrial Fibrillation, BMI=Body Mass Index

Table 2. Comparison of puncture characteristics and complications between groups

Variable	Group 1 (Control) (n=59)	Group 2 (Nitrate) (n=43)	Group 3 (Lidocaine) (n=40)	P value
Single puncture n (%)	29 (49.1)	33(76.7)	23 (57.5)	**0.018**
>2 puncture n (%)	30 (50.9)	10(23.3)	17 (42.5)	**0.018**
Femoral puncture n (%)	7 (11.8)	1(2.3)	3 (7.5)	**0.045**
Complications	24 (40.6)	4(9.3)	9 (22.5)	**0.010**
Spasm	9 (15.2)	3(6.9)	5 (12.5)	**0.043**
Hematoma	9 (15.2)	1(2.3)	3 (7.5)	**0.022**
Occlusion	5 (8.47)	0(0)	1 (2.5)	**0.041**
Pseudoaneurysm	0 (0)	0(0)	0 (0)	1.000
Dissection/rupture	0 (0)	0(0)	0 (0)	1.000
Compartment syndrome	0 (0)	0(0)	0 (0)	1.000
Puncture durations (seconds)	171±131	88±48	157±146	**0.002**
Puncture Count	2 (1-8)	1 (1-4)	1 (1-6)	**<0.001**

Data are shown as mean±standard deviation or n (%) or median (minimum-maximum).

group without cream application (Group 1) (P=0.675). Additionally, it was observed that there was a significantly lower number of punctures in group 2 as well (p<0.001). It was observed that the need for femoral procedure in group 2 significantly decreased compared to group 1 (P=0.045). In Group 1, the spasm was observed in 9 patients (15. 2%), and hematoma in 9 patients (15. 2%). Radial artery occlusion was observed in five patients (8.4%) in group 1. Complications developed in a total of 24 patients (40.6%) in Group 1, 4 patients (9.3%) in Group 2, and 9 patients (22.5%) in Group 3 (P=0.010). When comparing the

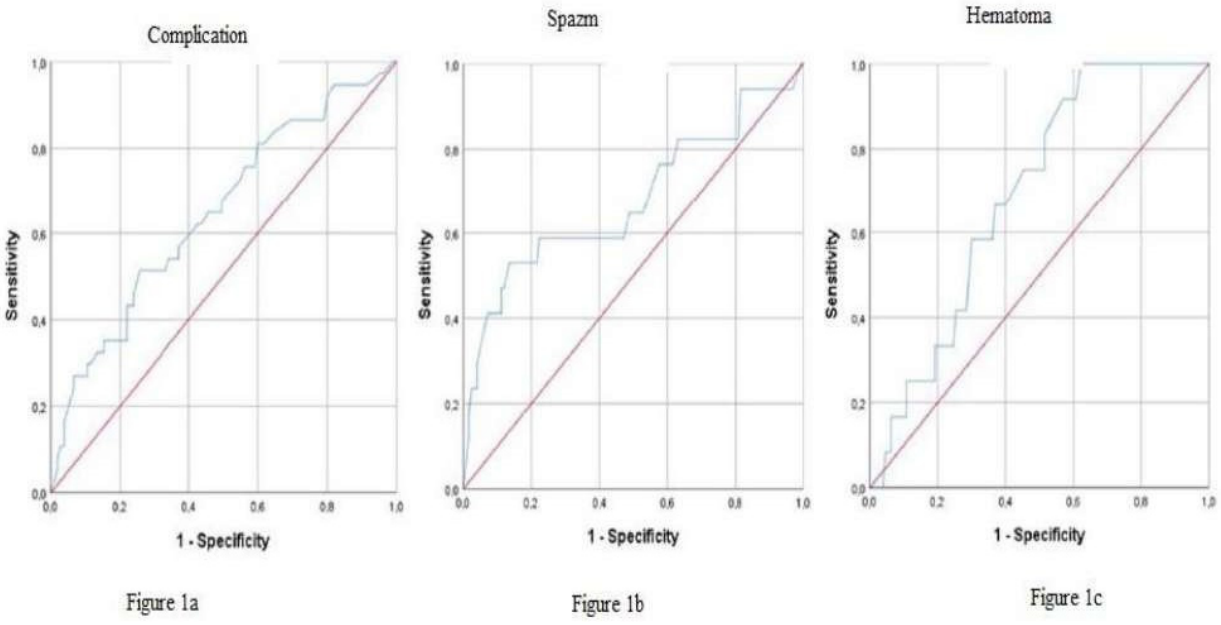

Fig. 1. Determination of puncture duration cut-off value on the development of complication.

complication rates among the three groups, it was found that spasm, hematoma, occlusion, and total complications were significantly less common in Group 2 (P<0.05). While the puncture time of 70 patients (49.3%) in the study group was 100 seconds or less, the puncture time of 72 patients (50.7%) was over 100 seconds.

When examining complications, in the group with puncture time exceeding 100 seconds, radial artery spasm occurred in 11 patients (15.3%), local hematoma in 9 patients (12.5%), and radial artery occlusion in 2 patients. In the group with a puncture time of 100 seconds or less, radial artery spasm occurred in 6 patients (8.6%), local hematoma in 3 patients (4.3%), and radial occlusion in 4 patients (5.7%). Although the rates of spasm and hematoma were higher in the group with puncture time over 100 seconds, and the occlusion rate was higher in the first group, these differences were statistically insignificant (P=0.218, 0.079, and 0.384, respectively). When considering total complications, in the group with longer puncture time (>100 seconds), complications were observed in 24 patients (33. 3%), while in the group with puncture time ≤100 seconds, complications were observed in 13 patients (18.6%), and this difference is statistically significant (P=0.045).

When the puncture time exceeds 104 seconds, it increases the risk of complications with a sensitivity of 62.2% and specificity of 57.1% (AUC=0.649; p=0.053). Looking at the subcategories of complications, when the puncture time exceeds 106 seconds, it also increases the likelihood of spasm with a sensitivity of 58.8% and specificity of 60% (AUC=0.678; p=0.082). Puncture time over 114 seconds increases the risk of regional hematoma with a sensitivity of 66.7% and specificity of 63.3% (AUC=0.691; P=0.060) (Figs. 1a, 1b and 1c). There was no significant difference between puncture time and radial occlusion.

DISCUSSION

According to the results of our study, topical nitroglycerin application is a feasible strategy to reduce radial puncture duration and number, facilitate trans-radial catheterization, and decrease the incidence of radial artery spasm and subsequent occlusion. Topical nitroglycerin effectively reduces both the number of radial artery punctures and the procedure duration.

Beyer *et al*. [6] study, which compared the effect of topical nitrate and lidocaine cream before transradial angiography in 83 patients, found that the group treated with nitrate + lidocaine cream had a 24% larger radial artery diameter compared to the control group, which was believed to reduce endothelial damage. However, unlike our study, radial artery spasms occurred in 25% of patients in both groups in this study, and no significant difference was observed. Some studies indicate that an increase in puncture attempts, pain at the access site, and spasms are risk factors for radial artery occlusion [7]. When the sheath size is larger than the arterial lumen, it may stretch the radial artery and cause endothelial damage. The rate of radial artery occlusion after arterial access seems to be related to the size of the radial sheath. While intra-arterial vasodilators used in our routine practice are applied after sheathing, endothelial damage begins with sheathing. Although the onset of action of topical nitrates is not as fast as intra-arterial application, topical nitrates are locally effective and have a longer duration of action. As dilation begins before sheathing, it is expected that there will be less endothelial damage.

A meta-analysis incorporating previous randomized controlled trials has shown that nitroglycerin administered subcutaneously reduces radial artery spasm and incidence of radial artery occlusion effectively [8]. Additionally, nitroglycerin has been effective in increasing radial artery diameter. Therefore, the prevention of radial artery spasm may subsequently lead to the prevention of radial artery occlusion. The variability in nitroglycerin dosage may also affect the findings. For example, regarding intra-arterial nitroglycerin dosage: both Dhrama *et al*. [8] and Da Silva *et al*. [9] used 500 µg. On the other hand, except for Coroleu *et al*. [10] who used 200 µg, the subcutaneous nitroglycerin dosage was 500 µg. Similarly, while subcutaneous nitroglycerin was effective in reducing spasms, intra-arterial nitroglycerin was not found to be effective.

In our study, nitroglycerin was effective in reducing radial artery puncture attempts and procedure duration. Multiple puncture attempts are the main cause of radial artery spasms. Our study suggests that the application of topical NTG half an hour before coronary angiography expands the artery diameter, increases

successful access in a single puncture, significantly reduces the number and duration of punctures, facilitates access to the radial artery, and significantly reduces the need for switching to an alternative artery by reducing endothelial damage and increasing the radial artery/sheath diameter to reduce spasm, thus reducing radial artery occlusion and associated complications.

The relationship between gender, age, body mass index, smoking and alcohol use, chronic diseases, and medications used was not shown to be associated with puncture duration. The prolongation of puncture duration has significantly increased complications. Puncture duration has been hypothesized as an important parameter in complications occurring at the sheath insertion site. A cut-off value for puncture duration was investigated, and ROC analyses revealed that a puncture duration exceeding 104 seconds predicted the risk of complications with 62.2% sensitivity and 57.1% specificity. When looking at the subcategories of complications, a puncture duration exceeding 106 seconds also increased the likelihood of spasm with 58.8% sensitivity and 60% specificity. A puncture duration exceeding 114 seconds increased the risk of regional hematoma with 66.7% sensitivity and 63.3% specificity. No significant relationship was found between puncture duration and radial occlusion.

Limitations

Differences in operator experience could potentially affect our results. Variations in puncture techniques and equipment used, especially differences in sheath size in trans-radial catheterization techniques, are reported as indicators of radial artery occlusion and could influence our results. Hemostasis protocols could also impact our findings. Furthermore, age-related atherosclerotic changes are also potentially confounding variables that we could not control for.

CONCLUSION

According to the findings of our study, topical nitroglycerin application emerges as a feasible and straightforward strategy to reduce radial puncture duration and frequency, facilitate trans-radial catheterization, and diminish the incidence of radial artery spasms and subsequent occlusion.

Authors' ContributionStudy

Conception: NU, AD; Study Design: NU, AD, ŞA; Supervision: AD, ŞA; Funding: NU, HA; Materials: NU, AD; Data Collection and/or Processing: NU, AD; Statistical Analysis and/or Data Interpretation: CA; Literature Review: CA, ŞA, HA; Manuscript Preparation: AD, CA and Critical Review: CA, HA.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2025;11(1):34-42 Original Article

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A different training model in providing effective medical waste management in the operating room: peer education

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ABSTRACT

Objectives: Objectives: This study aims to investigate the effectiveness of peer education methods in reducing medical waste in operating room settings.

Methods: A quasi-experimental design was utilized, involving 217 operating room staff who received training in medical waste management through a peer education program. Changes in knowledge, attitudes, behaviors, and the amount of medical waste generated before and after the intervention were evaluated.

Results: Following peer education, there was a significant increase in participants' knowledge levels regarding proper medical waste segregation. Positive shifts in attitudes and behaviors related to medical waste management were observed post-training. Additionally, the ratio of medical waste to general waste decreased, while the proportion of recyclable waste increased after the intervention.

Conclusions: Peer education emerges as an effective method for enhancing awareness and promoting proper medical waste management practices among operating room staff. However, achieving significant waste reduction requires comprehensive approaches beyond education alone. Clear regulations, improved infrastructure, and the adoption of reusable products are crucial for sustainable waste reduction efforts in healthcare settings.

Keywords: Medical waste management, peer education, operating room staff, waste reduction, behavior modification

Medical waste is defined by the World Health Organisation (WHO) as: "Waste generated in the processes of diagnosis, treatment or immunisation of humans or animals". Medical waste has a negative impact on the economies of countries and organisations as well as potential risks to human health. Problems in the proper disposal of these wastes increase the risk of infection and injury for healthcare personnel. In addition, it threatens public health by causing the spread of microorganisms from healthcare facilities to the environment [1-4].

An increase in the amount of medical waste is observed in connection with the increase in modern medical practices and easier access to healthcare services [5]. The use of disposable materials, which have the advantage of reducing the risk of infection between patients and healthcare personnel, further increases the production of medical waste, especially in developed

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countries. This leads to a rapid increase in the amount of medical waste that needs to be disposed of safely [6].

It is generally accepted that the best way to prevent non-infectious waste from entering the infectious waste stream is for staff working in healthcare facilities to segregate waste into infectious and non-infectious waste as soon as it is generated [7]. Health concerns and lack of knowledge lead to more medical waste generation. It has been found that most of the medical waste in the hazardous medical waste branch should not be thrown into the medical waste bag and cost savings of more than 30% can be achieved in this case with waste separation and correct definition of waste branches [8, 9].

Establishment of training programs to increase the awareness of perioperative staff members about medical waste may contribute to making positive behaviors about waste separation more widespread in the institutional culture and thus reducing the amount of medical waste [5, 10, 11].

Peer education is an active learning process in which it is aimed to change the knowledge, attitudes, beliefs and skills of individuals in a similar social group about a specific subject through educational activities by willing, volunteer and trained peers [12]. Peer education has a long history and has been used for different purposes to help the development of professional behaviors for groups of different ages and environments [13-15]. Nowadays, in the curricula of most medical schools, many departments and institutes adopt peer education method as a part of their daily teaching as well as problem-based learning [16, 17]. The aim of this study was to investigate the effect of peer education method on the reduction in the amount of medical waste.

METHODS

Study Design

Ethics committee permission was obtained from SBU Hamidiye Medical Faculty Ethics Committee with the decision dated 17.06.2022 and numbered 16/4 and local permission was obtained from Konya City Hospital Education Planning Board with the decision dated 02.12.2021 and numbered 12-16. The research conducted between 01.08.2022-02.12.2022 was descriptive and quasi-experimental. The population of the study consisted of 320 people consisting of anesthesia specialist and assistant doctors, anesthesia technicians, surgical nurses and table technicians working in the operating room. The sample consisted of 217 people who volunteered for the study.

A questionnaire form was prepared by the researchers after reviewing the relevant literature. This questionnaire aimed to evaluate the socio-demographic characteristics of the participants (8 questions) and their level of knowledge, thoughts and attitudes (12 questions) about medical waste generation, medical waste management. The questionnaire form created with Google Forms web application was delivered to the participants via social media (Whatsapp).

The amount of waste generated in our hospital is weighed separately for each clinic under the management of the environmental management department, separately as medical waste, domestic waste and recycling waste to be given to the company in charge of receiving medical waste every day. The amount of waste generated during the 35 days before the study started was obtained from the hospital environmental management department data. The team measuring the amount of waste did not know about this study.

Identification and Training of Peers

Inclusion criteria included working in our institution and operating room as anesthesiologists, assistant physicians, technicians, nurses, or housekeeping staff and having no language barriers in communication. Exclusion criteria included incomplete or inconsistent survey forms, unwillingness to participate, and not working during the study period due to reasons such as leave or medical report.

A standard medical waste training should include definitions related to the topic, scope, legal regulations, waste management processes, and health and safety issues. While planning the training with the employees working in the environmental management unit, they were asked to prioritize management processes and waste reduction topics. Additionally, fundamental issues related to medical waste management were also covered.

A pre-test on medical waste was first administered to the target group who volunteered to be included in the study. After this test, a peer trainer group was identified within the target group on a voluntary basis. Considering that each peer trainer could reach an av-

erage of 6-7 people, a group of 35 people was formed.

A peer trainer group consisting of 35 individuals received training twice. This training was provided by the same team from the environmental management unit, coordinated by the lead researchers. There was a 15-day interval between the two training sessions, and each session lasted 90 minutes.

The peer educator group was selected from people who were willing, had strong interpersonal communication, were respected by the target group and had non-judgmental attitudes (18,19). This group was ensured to be homogeneous in terms of profession and distribution to the operating rooms. The training included waste types, waste symbols, waste color coding, separation of medical waste at source. In addition, the contribution of this issue to the economy, waste disposal methods, the use of sharps boxes, injuries caused by medical waste, transmitted diseases, and the damage of waste on environmental health were explained. In addition to slides containing theoretical information, visual training methods such as short films were also used in the training.

A part of the training presentation was dedicated to the content and format of the training to be implemented by the peer trainers to ensure an effective and efficient learning experience. It was explained that during the training process, questions with missing information may be encountered, and in this case, accepting and expressing their deficiencies will increase the credibility and respectability of the learning environment, and that this attitude will help the group to develop a positive attitude towards learning and to establish a better interaction with the peer trainers. In this process, it was stated that it would be effective not only to transfer information to teammates but also to take on a supportive and motivating role in implementation. For two weeks after the training, peer trainers continued to work in the field in the form of sharing information, experience, reminders, and demonstrating exemplary behavior. Peer trainers did not use any standardized training materials while sharing their knowledge with other employees in the work environment. However, if needed, they used materials from their own existing trainings.

After the completion of the second part of the peer training, the amount of waste measured by the waste control unit was recorded again for 35 days. At the end of this 35-day period, a post-test with the same question content was administered to the entire target group. Pre-training and post-training tests were administered to all participants.

As the primary outcome of the study, the measurement of the amount of operating room medical waste before and 35 days after the peer education was evaluated. As a secondary outcome, the knowledge levels of the all participants after peer education were measured with five questions in the post-test and evaluated by comparing with the pre-test results. In addition, the behavior-attitude levels of the participants after peer education were measured with seven questions prepared according to the five-point Likert scale in the post-test and evaluated by comparing with the pre-test results.

Statistical Analysis

IBM SPSS Statistics (Version 24.0. Armonk, NY: IBM Corp.) program was used to evaluate the findings of the study. In our study, for sample size analysis, a 5% reduction after medical waste training was considered to be significant based on previous studies. In our 8-day pilot study conducted before the study, the mean medical waste in the group before the training was 403.51±22.89. In the independent groups t-test model created using the data of our pilot study, the partial Cohen's D effect size of 0.882 was used to calculate that 35 days of measurements should be performed in both groups for 95% power and maximum 5% type 1 error. Descriptive analyses such as percentage, mean and standard deviation were used for measurement values. Significance was evaluated at $P<0.05$ level.

RESULTS

The study included 217 operating room staff. Of the 217 participants, 115 (53%) were female, 108 (50%) had been practicing their profession for 1-5 years, and 146 (67%) had received previous training on the subject. The distribution of socio-demographic characteristics of the participants is given in Table 1.

The correct response rate to the question "In which waste bin should serum bags that do not come into contact with the patient be disposed of ?" increased from 90 to 125 (40% to 57.6%). However, the correct response rate to the question "In which waste bin should medication vials and serum bottles be disposed

Table 1. Socio-demographic characteristics of the participants

Characterisitics		n (%)
Gender	Female	115 (53)
	Male	102 (47)
Age (years)	18-25	88 (41)
	26-35	69 (32)
	36-45	40 (18)
	46-55	18 (8)
	55 ≥	2 (19)
Occupation	Surgical technician	35 (16)
	Nurse	64 (29)
	Anesthesia technician	71 (33)
	Anesthesiology resident	28 (13)
	Anesthesiologist	19 (9)
Gradution	High school	17 (8)
	Associate degree	72 (33)
	Bachelor degree	76 (35)
	Master's degree, medical faculty	36 (17)
	PhD, Specialist	16 (7)
Experience Period	<1	23 (11)
	1-5 years	108 (50)
	6-10 years	22 (10)
	11-15 years	28 (13)
	>15	36 (17)
Have you been trained on medical waste?	No	71 (33)
	Yes	146 (67)
Hepatitis vaccine history?	No	13 (6)
	Yes	193 (89)
	No answer	11 (5)
Have you had a tetanus vaccination in the last 5 years?	No	23 (11)
	Yes	176 (81)
	No answer	18 (8)

of?" was 15% before the training and increased to 27.6% after the training. A detailed analysis of the participants' answers to the knowledge questions about medical waste is given in Table 2.

"Do you consider your knowledge on medical waste sufficient?" The rate of respondents who considered their knowledge sufficient before the training decreased after the training (4.26 and 4, respectively). This difference is significant (P<0.01). Additionally, the rate of respondents who believed that the issue in medical waste segregation was due to a lack of knowledge was 3.71 before the training and decreased to 3.56 after the training. This difference is also significant (P<0.01). The comparison of the answers given to the 5-point Likert scale regarding the attitudes and behaviors of the participants with the paired t test is given in Table 3.

The change in the amount of weight before and after the training is given in Fig. 1. It was observed that the ratio of medical waste to all waste decreased from 8892,07 to 9569,41 (70% to 68%) in the post-training period, while this ratio increased from 1301,2 to 1485,48 (19% to 21%) in recycling waste, and there was no change in the ratio of household waste.

DISCUSSION

In our study, we investigated the effect of training given to operating room staff on medical waste management using the peer education method on the reduction in the amount of medical waste. We observed that the peer education method is an effective method in reducing the amount of medical waste.

Medical waste poses a risk of infection, contamination of soil and water resources, threats to ecosystems and disruption of the environmental balance, as well as negatively affecting the cost of institutions and countries. Waste generation rates vary according to the intensity of healthcare services, location (rural or urban), type of healthcare facility and clinic, size of use of disposable products, waste classification policies and regulations, segregation and reduction practices, procurement policies and development levels of countries [20]. Failure to segregate waste at its source and mixing it with domestic waste increases medical waste generation [21-23].

Reduction of waste generation is achieved through

Table 2. Pre-test and post-test results evaluating the participants' knowledge about medical waste

		Pre-test (n=217)	Post-test (n=217)
What is the biohazard symbol?			
	True	159 (73.3%)	161 (74.2%)
	False	49 (22.6%)	51(23.5%)
	No answer	9 (4.1%)	5 (2.3%)
In which waste bin should serum bags that do not come into contact with the patient be disposed of?			
	True	90 (40%)	125 (57.6%)
	False	126 (58.1%)	90 (41.5%)
	No answer	1 (18%)	2 (0.9%)
In which waste bin should medication vials and serum bottles be disposed of?			
	True	33 (15%)	60 (27.6%)
	False	181 (83.6%)	155 (71.4%)
	No answer	3 (1.4%)	2 (0.9%)
What is the most commonly used method for disposing of medical waste?			
	True	49 (22.6%)	76 (35%)
	False	68 (31.3%)	82 (37.8%)
	No answer	100 (46.1%)	59 (27.2%)
What color symbolizes medical waste?			
	True	209 (96.3%)	216 (99.5%)
	False	7 (3.2%)	1 (0.5%)
	No answer	1 (0.5%)	0 (0%)

Data are shown as n (%).

Table 3. Pre-test and post-test results evaluating the attitudes and opinions of the participants about medical waste

	Pre-test	Post-test	P value
Do the waste separation behaviours of the operating room team affect your attitudes?	3.45±1.09	3.65±1.34	0.10
Do you consider your knowledge on medical waste sufficient?	4.26±0.82	4.00±0.97	**<0.01**
Does peer education increase sensitivity to medical waste?	3.45±1.09	3.26±1.00	0.07
Do you think that information will have an effect on waste sorting?	4.42±0.92	4.11±0.95	**<0.01**
Is attention paid to the use of protective equipment?	3.71±1.12	3.56±1.09	0.15
Do you think that separating medical waste will have a cost impact?	4.42±0.84	4.48±0.86	0.47
Do you think there is a lack of information about medical waste segregation?	4.11±1.07	3.53±1.37	**<0.01**

Data are shown as mean±standard deviation. The answers are given on a 5-point Likert scale with 1: Strongly Disagree, 2: Disagree, 3: Undecided, 4: Agree, 5: Strongly agree, and 5: Strongly agree.

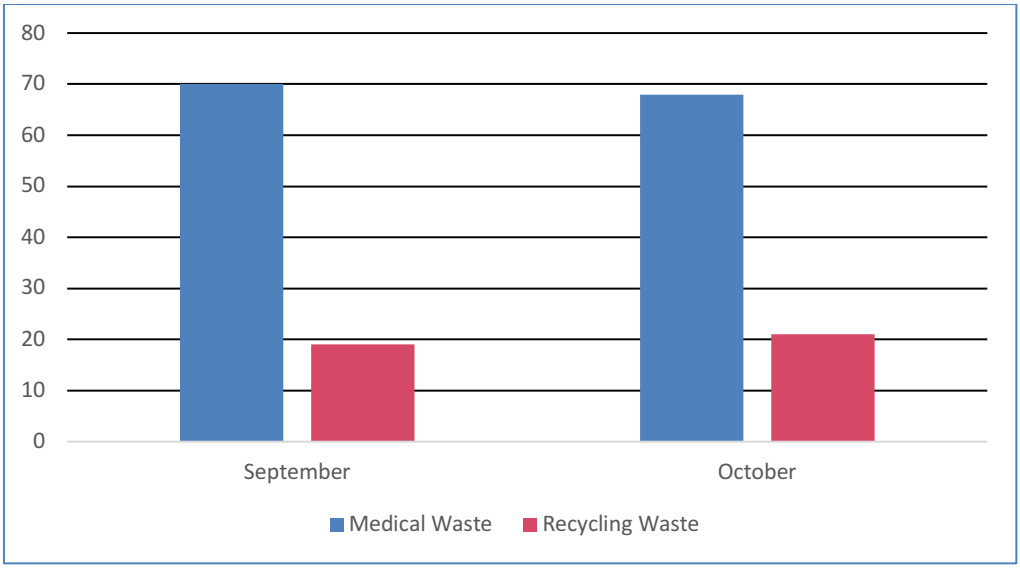

Fig. 1. The decrease in the ratio of medical and recycling waste to total waste before (September) and after (October) training.

three types of activities: absolute avoidance of waste generation, reduction at source and reuse of the product [24]. Effective personnel training is very important to reduce the amount of medical waste by segregation at the source [10]. In studies conducted with healthcare workers in our country, the rate of receiving training on medical waste varies between 43.5% and 70.7% [25-27]. In our study, the rate of receiving training on medical waste was found to be 67% and this result is consistent with the values previously reported in the literature.

Peer education programs offered as an alternative to traditional methods are used for different purposes and for groups of different ages and environments [13]. Studies have shown that the use of peer education method is effective in the skills/clinical training of nurse/medical students, teaching rational drug use, stoma care, breast self-examination, teaching physical examination in medical school, and organizing the perspective of mental illnesses [28-30]. In a study in which Chen and colleagues compared medical school students trained with traditional and peer education, it was found that the physical examination, written exam and peer evaluation scores of the students in the peer group were significantly higher [30].

In a study conducted by Öztürk *et al*. [31], five basic nursing skills that students learned for the first time were compared with peer education method and current teaching methods, and the rate of complete application of the skills within the scope of the research was found to be higher in the peer group compared to the control group.

There is no literature on the implementation of a peer education program on medical waste management and measuring the effects of this program. In our study, the results presented in Table 2 show that there was a significant increase in the knowledge level of the participants on how to properly separate medical waste after peer education. In particular, there was an increase in correct answers from 40% to 57% in the question of identifying the waste bin for serum bags that do not come into contact with the patient, and from 15% to 26.7% in the question of identifying the waste bins for drug vials and serum bottles. The peer education we conducted within the scope of this study shows that there is a significant increase in the knowledge level of the participants on how to correctly distinguish and properly dispose of medical waste materials. This shows that peer education can be used as an effective method to increase awareness on medical waste management and to enable healthcare personnel to play a more effective role in this field.

The pretest-posttest analysis of our study reveals that statistically significant differences were observed in the questions measuring attitude, behavior and thought (Table 3). These findings point to the potential of the training program to create a positive change in the participants' thoughts, attitudes and behaviors. In

particular, the fact that there were decreases in the positive answers given to the topics of considering their own knowledge sufficient, the effect of information on reducing medical waste generation and thinking that the problem in reducing medical waste is lack of information shows that the training increased the awareness of the participants on these issues. Our findings are in line with studies indicating that awareness rather than knowledge is weak in medical waste reduction.Hassan *et al*. revealed that medical waste problems arise due to lack of awareness and reluctance of healthcare workers and unclear policies and laws [32].

During the 35 days following the end of the training, the ratio of medical waste to general waste decreased from 70% to 68%, while the ratio of recyclable waste increased from 19% to 21% (Fig. 1).

Dönmez and Keskin [11] found that while the amount of medical waste decreased after training, there was a statistically significant increase in the amount of recycling waste and piercing-cutting waste. In the study of Almuneef and Memish [9], a 50 percent decrease was observed in the amount of medical waste after the implementation of a medical waste management plan and this rate is considerably higher compared to our study. The implemented medical waste management plan included mandatory in-service training, placement of color-coded waste bags in relevant areas, and waste type control. The fact that segregation was implemented for the first time in the hospital increased the rate. In our hospital, color-coded sorting was already in place, and there were 2 boxes each for medical waste, recycling, household waste, sharps, hazardous waste in each operating room. This may be effective in our medical waste reduction rate being lower.

In a study of Conrardy *et al*. [33], they conducted between two large medical centers in Bethesda, Maryland and Washington DC, medical waste produced in the operating room decreased by an average of 65% after reusable materials were preferred in surgical applications. By choosing reusable products, a significant reduction in the amount of waste caused by disposable products is achieved. This project emphasizes the importance of using reusable products as a way to reduce environmental impacts and lower costs in surgical practices. This suggests that factors other than education and awareness are effective in reducing medical waste.

Windfeld and Brooks [34] found that while many developed countries have legislation, there is often little guidance on what objects can be defined as infectious, and this lack of clarity leads to increased volumes of medical waste. Most studies in the literature have found that most of the waste generated by hospitals is not infectious and can therefore be disposed of in municipal landfills and recycling programs [35].

Lack of sufficient knowledge, awareness and clarity in medical waste legislation may lead to more medical waste generation due to health concerns and safety. It is important to clearly define the scope of legal regulations and the definition of infectious waste in medical waste reduction. In hospitals that have not been previously trained in medical waste management and whose rules are not clear, making these arrangements together with training can lead to serious reductions in the amount of waste, while in hospitals that have established this system, the contribution of training to waste reduction may be less.

Limitations

The most important limitation of our study was the small number of participants and the fact that the study area included only one hospital. The second limitation is that medical waste education with peer education method was not evaluated comparatively with a control group. However, the fact that all operating room personnel worked in circulation in a common area did not allow the formation of separate groups. Our third limitation was the exclusion of surgical physicians and cleaning staff who collect and carry the waste bins. The reason for not including them was that cleaning personnel are regularly trained by the environmental management unit, while the high circulation of surgical physicians would prevent effective training. In addition, being in the same environment during the activities of volunteer peer trainers has the potential to provide training and awareness for the whole team.

CONCLUSION

In conclusion, although peer education is an effective method for segregation of medical waste at source, more than knowledge is required for knowledge to lead to behavioral change to a great extent. In order to achieve a significant reduction in the rate of medical

waste, multifaceted regulations are needed in addition to peer education.

Authors' Contribution

Study Conception: NAE; Study Design: NAE; Supervision: MAY; Funding: MAY; Materials: BK; Data Collection and/or Processing: BK; Statistical Analysis and/or Data Interpretation: SU; Literature Review: SU; Manuscript Preparation: NAE and Critical Review: NAE.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Clinical and electrocardiographic predictors of left ventricular diastolic dysfunction in patients with idiopathic premature ventricular contractions

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ABSTRACT

Objectives: Tachycardiomyopathy is a well-known phenomenon with reduction in left ventricular (LV) systolic function. In our study, we aimed to investigate the effects of idiopathic premature ventricular contractions (PVCs) on LV diastolic function in patients with idiopathic PVCs.

Methods: We included 63 patients who are candidates to undergo radiofrequency ablation due to idiopathic PVCs (27 male, 36 female; mean age 47.9±16.6 years). Patients were classified into two groups according to the presence of LV diastolic dysfunction. The percentage of PVC burden was calculated by dividing the daily PVC burden by the total heart beat per day. Coupling interval ratio was calculated with the formula of Coupling interval ratio = (Coupling interval/sinus cycle length) 100.

Results: Age, presence of q wave in D2-D3, daily PVC burden, percentage of PVC burden, left atrial volume index, intervenricular septum thickness, and mitral E/e' ratio were significantly higher; male gender, peak E-wave velocity, lateral and septal annular e' velocity were significantly lower in patients with LV diastolic dysfunction. Daily PVC burden and percentage of PVC burden were positively correlated with mitral E/e' ratio and negatively correlated with lateral annular e' velocity. The coupling interval ratio was positively correlated with mitral E/e' ratio. Age, daily PVC burden, and percentage of PVC burden were independent predictors of increased mitral E/e' ratio. The cutoff value of the percentage of PVC burden was 15.59% for prediction of LV diastolic dysfunction (sensitivity: 88.9%, specificity: 66.7%).

Conclusions: Daily PVC burden, percentage of PVC burden, and coupling interval ratio are correlated with echocardiographic parameters of LV diastolic function.

Keywords: Premature ventricular contractions, coupling interval ratio, left ventricular diastolic function

Idiopathic premature ventricular contractions (PVCs) have been demonstrated to have detrimental effects on cardiac hemodynamics and are associated with a reduction in left ventricular (LV) function [1]. Tachycardia-induced cardiomyopathy or tachycardiomyopathy is a well-known phenomenon that describes LV systolic dysfunction due to PVCs [1]. Previously defined risk factors for LV systolic dysfunction in patients with idiopathic PVCs are high frequency of PVCs, short coupling intervals of PVCs,

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increased PVC QRS duration, and absence of PVC-associated symptoms such as palpitations [2-4].

Although idiopathic PVCs are usually well tolerated in patients with normal cardiac function, not only LV systolic function but also diastolic function has been adversely affected in recent studies [5-7]. These adverse effects may cause a deterioration of the left atrial (LA) structure and function, and may also trigger new-onset atrial arrhythmias such as atrial fibrillation [8]. In our study, we aimed to investigate the effects of idiopathic PVCs on LV diastolic function and predictors of LV diastolic dysfunction in patients who are candidates to undergo radiofrequency (RF) ablation due to idiopathic PVCs.

METHODS

Study Population

We included 63 patients who are candidates to undergo RF ablation with a 3D electroanatomic mapping system due to idiopathic PVCs (27 male, 36 female; mean age 47.9±16.6 years). Patients older than 18 years old with predominant PVCs exhibiting ECG characteristics suggestive of outflow tract or other typical locations for idiopathic PVCs, frequent PVCs (>10% daily PVC burden) according to 24-hour Holter ECG monitoring, patients with symptoms associated with PVCs were included in the study. In order to eliminate negative effects on LV diastolic function, patients with permanent atrial fibrillation (AF), hypertension, diabetes, renal insufficiency (serum creatinine >1.5 mg/dL), respiratory diseases (chronic obstructive pulmonary disease [COPD], chronic bronchitis, pulmonary embolism), primary pulmonary hypertension, history of coronary artery disease, isolated right heart failure, congenital heart disease, moderate and severe aortic and mitral valve disease were excluded from the study. Patients were classified into two groups according to the presence of LV diastolic dysfunction. All statistical analyses were made between the two groups. The Local Ethics Committee approved the study protocol (decision no.:06, date:12.11.2020), and each participant provided written informed consent. After assessment of detailed medical history and a complete physical examination, the baseline characteristics of patients including age, sex, family history of cardiac disease and medications were recorded for all patients. Electrocardiogram (ECG), fasting blood glucose, renal function tests were performed.

Echocardiographic Assessment

The echocardiographic assessment was performed using parasternal long and short axis, apical two and four-chamber views with a 2.5-3.5 MHz transducer (Philips HD11 ultrasound system, Bothell, USA) [9]. LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV), and LV ejection fraction (LVEF) were assessed using Simpson's equation using the apical 4-chamber view. PW Doppler and color tissue Doppler evaluation were performed to determine LV diastolic functions. Indices of LA volumes for body

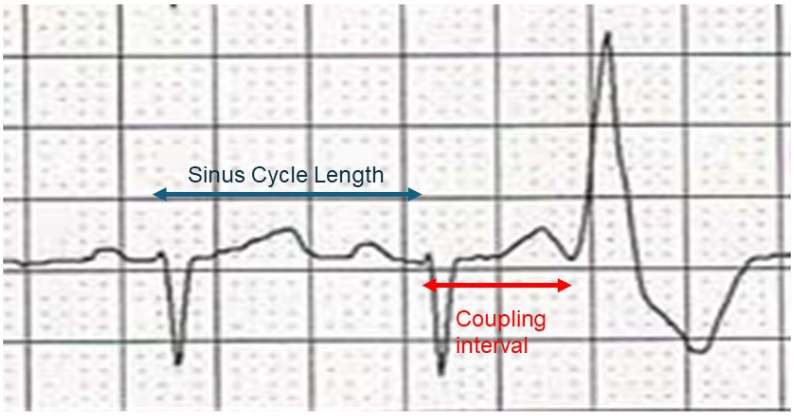

Fig. 1. Calculation of coupling interval ratio.

surface area were also calculated. All echocardiographic measurements were made during sinus rhythm and pre-PVC and post-PVC intervals were not used for measurements. LV diastolic dysfunction was defined as the presence of one of these three criterion: 1] mitral E/A ratio ≤0.8 or ≥2.2] average mitral E/e' ratio >14, 3] Septal e' velocity <7 cm/s or lateral e' velocity <10 cm/s according to the suggestions of ASE/EACVI 2016 guidelines for evaluation of LV diastolic function by echocardiography [10].

24-Hour Holter ECG Monitoring and Electrocardiographic Assessment

24-hour rhythm holter monitorization was made with DMS 300-3A EKG Holter Recorder (DM Software NV, USA). Patients were informed about the device and then were sent to their homes. After 24 hours, the device was removed and the recordings were analyzed and concluded with the program DM Software Cardio Scan 2 premier. Holter parameters were recorded and the data of patients and controls were compared. Total heart beat per day and daily PVC burden were detected. The percentage of PVC burden was calculated by dividing the daily PVC burden by the total heartbeat per day. The QRS duration of PVC was defined as the length of time from the beginning to the end of the QRS complex in the lead with the widest QRS complex. The maximum deflection index was calculated with this formula: (interval between the onset of QRS and earliest point of maximum deflection in V5-V6) / (total QRS duration). The coupling interval of PVCs was measured from the onset of the QRS of the previous sinus beat to the onset of the PVC QRS. Coupling interval ratio was calculated with the formula of: Coupling interval ratio = (Coupling interval/sinus cycle length) × 100 (Fig. 1).

Statistical Analysis

Statistical analyses were conducted using SPSS, version 21.0, (SPSS Inc. Chicago, Illinois). Data are expressed as mean ± standart deviations for continuous variables and percentage for categorical variables. The Shapiro-Wilk test was used to test normality. The Student t-test was used for continuous variables with normal distribution and the Mann-Whitney U test was used for continuous variables with non-normal distribution. Categorical variables and frequencies were compared with the chi-square test. Statistical significance was defined as a P-value <0.05 for all comparisons. Pearson's and Spearman's correlation were used to examine the relationship between continuous variables.

The factors associated with increased mitral E/e' ratio were tested in multivariate linear logistic regression analyses. Variables with a P-value <0.05 in the

Table 1. Comparison of baseline clinical, ECG, and 24-hour holter monitoring parameters in patients with and without left ventricular diastolic dysfunction

	Patients without LVDD (n=37)	Patients with LVDD (n=26)	P value
Age (years)	42.8±16.1	54.0±15.5	**0.022**
Gender (male), n (%)	23 (62)	4 (15)	**<0.001**
Q wave in D1, n (%)	13 (35)	8 (31)	0.717
Q wave in D2-D3, n (%)	5 (13)	9 (35)	**0.047**
PVC QRS width (ms)	173.6±23,0	170.4 ±24.1	0.601
Intrinsicoid deflection time (ms)	96.2±21.4	95.5±25.5	0.993
Maximum deflection index	0.55±0.13	0.56±0.15	0.820
Coupling interval (ms)	461.8±67.8	474.7±82.5	0.523
Coupling interval ratio (%)	62.12±9.78	64.78±11.43	0.354
Daily PVC burden (beats/day)	16793±11848	27488±15490	**0.042**
Percentage of PVC burden (%)	14.9±9.6	23.9±11.3	**0.029**

Data are shown as mean±standart deviation or n (%). LVDD=left ventricular diastolic dysfunction, PVC=Premature ventricular contraction, Coupling interval ratio = (Coupling interval/sinus cycle length) x 100

univariate analysis were tested in the multivariate model. ROC analysis was made to determine the cut-off value of the coupling interval ratio for LV diastolic dysfunction.

RESULTS

Comparison of Baseline Parameters

A comparison of the baseline clinical, ECG, and 24-Hour Holter monitoring parameters is shown in Table 1. Age, Q wave in D2-D3, daily PVC burden, and percentage of PVC burden were significantly higher; male gender was significantly lower ($p<0.05$, for all) in patients with left ventricular diastolic dysfunction. LA volume index, IVS thickness, and mitral E/e' ratio were significantly higher; peak E-wave velocity, lateral and septal annular e' velocity were significantly lower ($P<0.05$, for all) in patients with left ventricular diastolic dysfunction (Table 2).

Bivariate and Multivariate Correlations

Age was positively correlated with mitral E/e' ratio (r=0.301, P=0.045), and negatively correlated with mitral E/A ratio (r=-0.383, P=0,009), lateral annular e' velocity (r=-0.504, P<0.001) and septal annular e' velocity (r=-0.457, P=0.002) in bivariate analysis (Table 3). Daily PVC burden was positively correlated with mitral E/e' ratio (r=0.545, P=0.002), and negatively correlated with lateral annular e' velocity (r=-0.401, P=0.023). The percentage of PVC burden was positively correlated with mitral E/e' ratio (r=0.489, P=0.005), and negatively correlated with lateral annular e' velocity (r=-0.402, P=0.022). The coupling interval ratio was positively correlated with the mitral E/e' ratio (r=0.371, P=0.006), A scatter plot diagram of the relationship between the coupling interval ratio and mitral E/e' ratio is shown in Fig. 2. Multivariate linear regression analysis showed that age (β=0.103, P=0.001), daily PVC burden (β=0.001, P=0.004), and percentage of PVC burden (β=-1.164, P=0.010) were

Table 2. Comparison of the baseline echocardiographic features of the study population

Variable	Patients without LVDD (n=37)	Patients with LVDD (n=26)	P value
LV end-diastolic diameter (mm)	49.2±10.2	50.2±8.8	0.686
LV end-systolic diameter (mm)	34.0±11.6	36.9±10.0	0.313
LVEF (%)	55.4±14.6	51.9±16.1	0.375
LVEDV (mL)	106.3±42.8	120.1±55.5	0.271
LVESV (mL)	54.3±33.3	58.2±36.4	0.667
Peak E-wave velocity (cm/s)	83.5±16.7	70.9±19.8	**0.010**
Peak A-wave velocity (cm/s)	67.1±15.7	78.7±30.1	0.051
MV E/A ratio	1.30±0.3	1.05±0.6	0.063
Lateral annular e' velocity(cm/s)	14.0±2.3	7.9±2.6	**<0.001**
Septal annular e' velocity(cm/s)	10.9±2.2	8.2±2.8	**<0.001**
Mitral E/e' ratio	6.8±1.8	9.5±4.1	**0.005**
IVRT (ms)	79.1±19.,1	87.2±19.6	0.104
IVS thickness (mm)	9.9±1.8	12.6±3.2	**<0.001**
PW thickness (mm)	9.4±2.2	9.7±3.2	0.708
LA end-diastolic diameter (mm)	32.1±5.1	34.4±5.7	0.129
LA volume index (mL/m²)	31.5±16.7	41.2±12.8	**0.040**

Data are shown as mean±standart deviation. LVDD=left ventricular diastolic dysfunction, LV=Left ventricle, LVEF=Left ventricle ejection fraction, LVESV=Left ventricle end-systolic volume, LVEDV=Left ventricle end-diastolic volume, IVRT=Isovolumetric relaxation time, MV=Mitral valve, LA=Left atrium, IVS=interventricular septum, PW=posterior wall

Table 3. Correlation analysis of the continuous variables associated with LV diastolic function

Variables	Mitral E/A ratio	Lateral annular e' velocity	Septal annular e' velocity	Mitral E/e' ratio	LA volume index
Age (r)	**- .383****	**- .504*****	**- .457****	**.301***	.123
Daily PVC burden (r)	.115	**- .401***	- .306	**.545****	.279
Percentage of PVC burden (r)	.065	**- .402***	- .280	**.489****	.295
PVC QRS width (r)	- .230	- .078	- .176	.090	.195
Maximum deflection index (r)	.196	.033	.097	- .093	- .184
Coupling interval (r)	- .014	- .262	- .241	.268	.113
Coupling interval ratio (r)	.266	-.087	- .163	**.371****	.002

Coupling interval ratio = (Coupling interval/sinus cycle length) × 100
*P<0.05, **P<0.01, ***P<0.001

independent predictors of increased mitral E/e' ratio (Table 4).

ROC Curve Analysis to Determine the Predictive Value of Coupling Interval Ratio for LV Diastolic Dysfunction

The cutoff value of the percentage of PVC burden obtained by ROC curve analysis was 15.59% for prediction of left ventricular diastolic dysfunction (sensitivity: 88.9%, specificity: 66.7%). The area under the curve (AUC) was 0.745 (P=0.032) (Fig. 3).

DISCUSSION

To our knowledge, this is the first study to investigate the association of ECG characteristics of PVCs and LV diastolic dysfunction. The main findings of the present study are that: [1] Daily PVC burden, percentage of PVC burden, and coupling interval ratio were correlated with echocardiographic parameters of LV diastolic function such as lateral annular e' velocity and mitral E/e' ratio in bivariate analysis. [2] PVC burden (15.59%) predicts left ventricular diastolic dys-

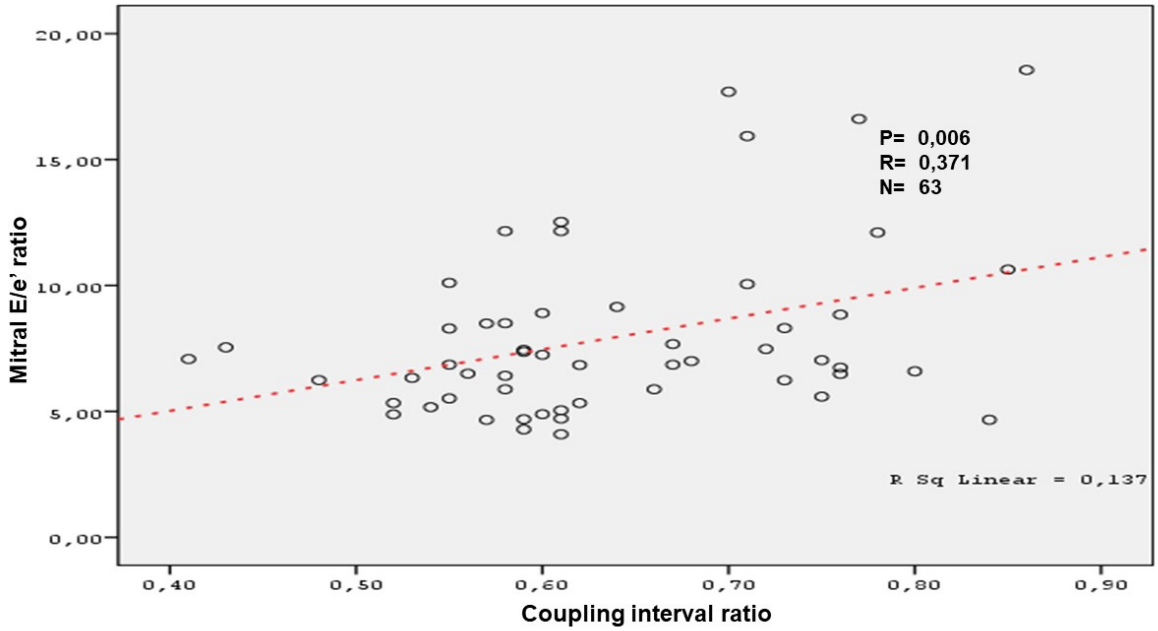

Fig. 2. Scatter plot diagram of the relationship between coupling interval ratio and mitral E/e' ratio.

Table 4. Multivariate linear regression to detect independent predictors of high mitral E/e' ratio

Variables	Standardized β-regression coefficients	P value
Age	0.103	**0.001**
Daily PVC burden	0.001	**0.004**
Percentage of PVC burden	-1.164	**0.010**
Coupling interval ratio	0.154	0.261

Coupling interval ratio: Coupling interval / Sinus Cycle Length, PVC=prematüre ventricular contraction

function with 88.9% sensitivity and 66.7% specificity.

PVCs are the most common cardiac arrhythmias. The patient population with PVCs is expanding with the widespread use of long-term ECG Holter monitoring devices. Detrimental effects of idiopathic PVCs on LV systolic function which is also known as tachycardia-induced cardiomyopathy is well documented. The factors associated with tachycardia-induced cardiomyopathy are widely investigated. Previously defined risk factors for LV systolic dysfunction in patients with idiopathic PVCs are high frequency of PVCs, short coupling intervals of PVCs, increased PVC QRS duration, and absence of PVC-associated symptoms such as palpitations [2-4]. In our study, we found a high PVC burden (15.59%) and a high coupling interval ratio to be associated with a high mitral E/e' ratio. In contrast to the fact that short coupling intervals of PVCs are a well-documented risk factor for tachycardiomyopathy, in our study, we found a long coupling interval ratio to be associated with LV diastolic dysfunction. This may be due to the negative effects of retrograde atrioventricular (AV) conduction and retrograde atrial depolarization on LA electrical and mechanical functions. Longer coupling intervals may increase the chance of retrograde AV conduction by providing enough time for the AV junction to be conductive after the refractory period of the previous sinus beat. Retrograde AV conduction and retrograde atrial

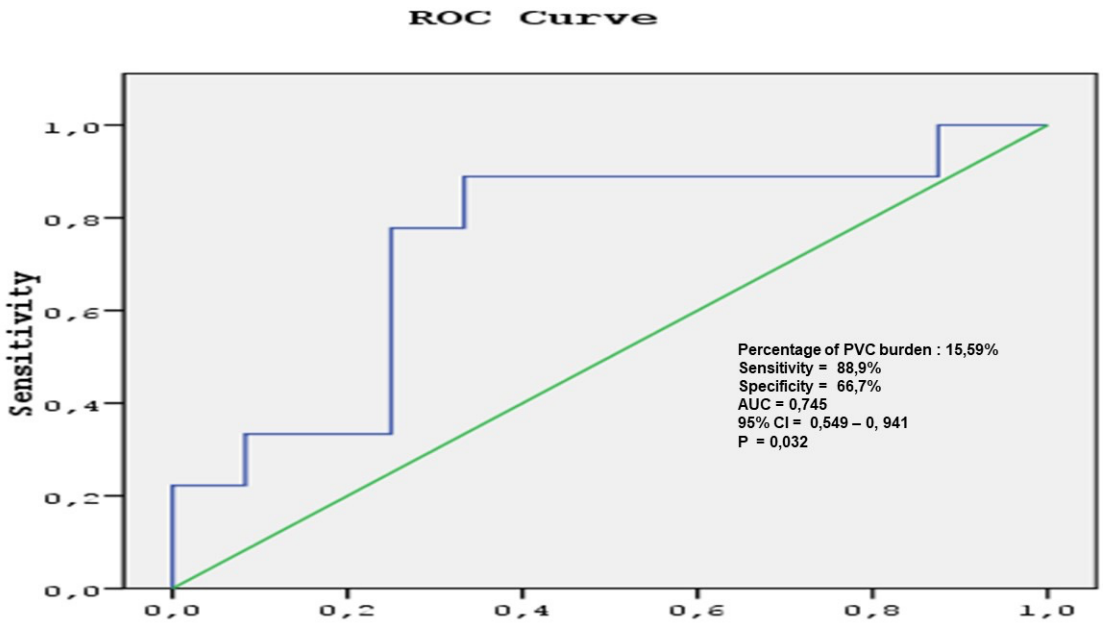

Fig. 3. ROC curve analysis to determine predictive value of percentage of PVC burden for left ventricular diastolic dysfunction. PVC=prematüre ventricular contraction.

depolarization after PVCs may cause dyssynchrony on LA contraction and may also disrupt atrioventricular synchrony if LA construction occurs when AV valves are closed. This condition further increases LV filling pressures. Similarly, in a recent study, the coupling interval ratio was found to be higher in patients who had PVC-related symptoms compared to the patients without symptoms even though PVC burden and age were similar between the two groups [11]. In this case, further studies are needed to clarify the relationship between new-onset AF and longer coupling intervals of PVCs.

Despite their benign nature, the risk of cardiovascular mortality increases with higher burdens of idiopathic PVCs [12, 13]. Interestingly, PVCs have been demonstrated to trigger atrial fibrillation when there is retrograde AV conduction [14, 15]. The study of Ofoma *et al*. [16] which demonstrates the association of PVCs with ischemic stroke also emphasizes the importance of the aforementioned mechanism of AF pathophysiology. Recent studies demonstrated that clinical diagnosis of PVC increases the risk of new-onset AF [17]. In a large population-based study, moderate-to-high burden PVCs (≥1000/day) were found to have a higher risk of developing new-onset AF than the low-burden PVCs (4.91% versus 2.73%, P<0.001) [8]. In our study, we found high PVC burden and high coupling interval ratio to be associated with high LV filling pressures. As increased LV filling pressure is associated with left atrial mechanical and electrical remodeling, AF occurrence can be thought to be the next step in this pathophysiological process.

Limitations

There were some limitations in our study. The sample size is relatively small and our results need to be confirmed in future large multi-center prospective trials. Since our study was not a follow-up study, we could not determine the change of LV systolic and diastolic function after successful PVC ablation procedure.

CONCLUSION

Daily PVC burden, percentage of PVC burden, coupling interval ratio were correlated with echocardiographic parameters of LV diastolic function such as lateral annular e' velocity and mitral E/e' ratio. We suggest that larger and long term studies are needed to determine the relationship between clinical and electrocardiographic factors and AF occurrence in patients with idiopatic PVCs.

Ethics Approval

The study was reviewed and approved by the MKU Tayfur Ata Sökmen Medical Faculty Clinical Research Ethics Committee (Decision number: 06 and date: 12.11.2020).

Authors' Contribution

Study Conception: OK, FÖS; Study Design: OK, FÖS; Supervision: OK, FÖS; Funding: N/A; Materials: FÖS; Data Collection and/or Processing: FÖS; Statistical Analysis and/or Data Interpretation: FÖS; Literature Review: OK; Manuscript Preparation: OK and Critical Review: FÖS.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

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The European Research Journal 2025;11(1):51-56 Original Article

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Evaluation of bismuth shielding in reducing thyroid radiation dose during neck multidetector computed tomography examinations: a comparative study

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ABSTRACT

Objectives: This study pointed to assess the viability of bismuth protecting in lessening thyroid radiation measurements amid neck multidetector computed tomography (MDCT) examinations and to explore alternative protecting strategies which will moderate negative impacts on picture quality.

Methods: The study involved 20 patients undergoing neck MDCT. Thermoluminescent dosimeters (TLDs) were utilized to degree radiation measurements to the thyroid organ with and without bismuth protecting. Measurable investigations, counting combined tests t-test and Wilcoxon signed-rank test, were conducted to evaluate the importance of dosage decrease.

Results: Bismuth protecting altogether diminished the radiation measurements to the thyroid organ by 43.95%, from 24.50 mGy to 17.59 mGy ($P<0.01$). The reduction was statistically significant in women ($P<0.01$) but not in men ($P>0.05$) due to the small sample size. No significant correlation was found between age and radiation dose levels ($P>0.05$).

Conclusions: Bismuth shielding effectively reduces thyroid radiation dose during neck MDCT examinations. However, the potential increase in image noise necessitates careful management to maintain diagnostic accuracy. Further research is needed to optimize shielding techniques and explore alternative methods to minimize radiation exposure while preserving image quality.

Keywords: Bismuth shielding, thyroid radiation dose, neck MDCT, radiation protection

All living organisms are continuously exposed to natural radiation throughout their lives. This exposure includes billions of particles and photons from cosmic rays and radionuclides present in the earth's crust, which pass through our bodies daily. In addition to natural sources, humans are exposed to man-made radiation, primarily from medical procedures, which accounts for approximately 15% of total radiation exposure [1]. Radiation can be categorized into ionizing and non-ionizing types, with ionizing radiation, such as X-rays and gamma rays, having the potential to cause significant biological damage due to its ability to ionize atoms and molecules within cells [2].

The fast progressions in computed tomography (CT) innovation over the past decade have driven a

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noteworthy increment within the number of CT examinations and the volume of body locales filtered. CT constitutes almost 5% of all radiological examinations worldwide, accounting for one-third of therapeutic radiation presentations [3]. Despite its diagnostic benefits, CT imaging poses a substantial risk due to the high radiation doses involved, particularly to radiosensitive organs like the thyroid gland. The thyroid is especially vulnerable during neck CT scans, where it can receive doses significantly higher than those from conventional radiography [4].

Bismuth shields have been introduced as a protective measure to reduce radiation exposure to the thyroid during CT examinations. These protective barriers are capable of reducing the radiation exposure to the thyroid gland by roughly 30-60% [5, 6]. However, their employment is controversial because of possible negative impacts on image clarity, including heightened noise and distortions, which might undermine the accuracy of diagnoses [7]. Due to these drawbacks, the American Association of Physicists in Medicine (AAPM) has recommended against the routine use of bismuth shields [8].

Given these concerns, alternative methods such as the Saba shield have been explored. The Saba shield, which combines copper and bismuth, offers a promising solution by reducing radiation exposure without significantly affecting image quality [9]. The objective of this research is to assess how well bismuth shielding can decrease the amount of radiation exposure to the thyroid during neck multidetector computed tomography (MDCT) scans, while also investigating different shielding techniques that could lessen adverse effects on image clarity.

The primary goal of this study was to examine how radiation exposure to the thyroid gland varies during neck MDCT scans, especially when comparing procedures done with and without the use of bismuth shields. To achieve precise measurements, thermoluminescent dosimeters were employed. Additionally, the research aimed to determine the overall amount of radiation the thyroid gland receives during these diagnostic tests. From October to December 2007, twenty patients who needed neck MDCT scans at our facility were included in this research. The findings from this study are vital, offering significant insights into how effective bismuth shielding is at reducing radiation exposure to the thyroid.

METHODS

Study Design and Sample

This research was carried out following the approval from the institutional ethics committee, and informed consent was secured from all participants. The research was carried out between October 2007 and December 2007 at the Radiology Department of an university hospital. A total of 20 patients (9 males and 11 females, aged 28 to 70 years, with a mean age of 52) who were referred for neck MDCT were included in the study. The primary aim of this study was to evaluate the differences in radiation exposure to the thyroid gland with the application of bismuth shielding versus without, employing thermoluminescent dosimeters (TLDs) for measurement. Additionally, the study sought to quantify the total radiation dose received by the thyroid throughout MDCT procedures.

Imaging Protocol

MDCT imaging was conducted utilizing a Siemens Sensation Cardiac scanner (Sensation 16, Siemens, Forchheim, Germany). The parameters set for the scanning procedure encompassed a detector collimation of 15, a gantry rotation duration of 0.75 seconds, an X-ray tube potential of 120 kV, and a tube current measuring 230 mAs. The slice thickness was set to 5 mm, and the average field of view (FOV) was 20 cm. Patients were positioned supine on the gantry, and images were acquired from the occiput to the thoracic inlet, covering the cervical region.

Dosimetry

For each patient, a pair of thermoluminescent dosimeters (dimensions: 3x3x1 mm; manufactured by Harshaw Lif TLD-100 and Saint-Gobain Industrial Ceramics, Solon, Ohio) were employed. The TLDs were placed on the estimated thyroid tissue, 2.5 cm inferior to the central prominence of the thyroid cartilage and 2 cm lateral to the midline, parallel to the long axis of the cervical spine. One TLD was covered with a bismuth shield, while the other was left uncovered, allowing for a direct comparison of radiation doses between the shielded and unshielded sides of the thyroid.

Statistical Analysis

The measurement of the radiation dose absorbed by the thyroid gland was carried out through TLDs,

Table 1. Evaluation by gender

TLD average dose (mGy)	Mean±SD	Median	P value
Women (n=11)			
Shielded side	15.97±5.97	15.2	**0.003**
Unshielded side	23.69±9.07	20.1	
Men (n=9)			
Shielded side	19.56±6.32	18.3	0.051
Unshielded side	25.50±8.00	21.9	

TLD= thermoluminescent dosimeter, SD=standard deviation
Wilcoxon signed-rank test was used.

with an evaluation of the bismuth shield's efficiency in mitigating this dose. Statistical analyses were executed employing NCSS 2007 & PASS 2008 Statistical Software, based in Utah, USA. This included the computation of descriptive statistics, such as the mean and standard deviation. For the comparison of normally distributed quantitative data, the paired samples t-test was utilized, whereas the Mann-Whitney U test and the Wilcoxon Signed Rank test were employed for data that did not follow a normal distribution. Additionally, Pearson correlation analysis was performed to examine the linkage between the age of the subjects and the received radiation dose. A P-value below 0.05 was established as the threshold for statistical significance.

RESULTS

This research sought to assess the effect of bismuth shielding on the amount of radiation absorbed by the thyroid gland during neck MDCT scans. The use of TLDs allowed for precise measurement of radiation exposure, comparing the shielded and unshielded lobes of the thyroid.

The results demonstrated a statistically significant reduction in radiation dose to the thyroid gland when bismuth shielding was applied. The average TLD dose for the shielded side was 17.59±6.24 mGy, compared to 24.50±8.43 mGy for the unshielded side, indicating a reduction of 43.95%±28.72% (P<0.01). This substantial reduction highlights the efficacy of bismuth shields in mitigating radiation exposure to organs sensitive to radioactivity.

The percentage reduction in TLD average dose for the shielded side compared to the unshielded side was calculated as 43.95%±28.72%.

In females, the mean dose of TLD for the side protected by shielding was markedly less in comparison to the side without protection, with the difference being statistically significant (P=0.003). In males, the mean dose on the shielded side was also reduced; however, this reduction did not achieve statistical significance, which could be attributed to the limited size of the sample (P>0.05).

The study indicated no substantial disparity in the average doses of TLD for both males and females, regardless of whether the measurement was taken on the shielded or unshielded sides, as evidenced by a P-value greater than 0.05 (Table 1).

There was no statistically significant association identified between age and the average dose levels of TLD on both the shielded and unshielded sides, as evidenced by a p-value greater than 0.05 (Table 2).

DISCUSSION

In our study, we investigated the average radiation exposure of the thyroid gland in 20 patients referred to

Table 2. Correlation between age and TLD average dose

TLD average dose (mGy)	r	P value
Shielded side	0.221	0.348
Unshielded side	0.355	0.124

TLD= thermoluminescent dosimeter
Pearson correlation analysis was used.

our department for neck MDCT scans. Our analysis focused on evaluating the effectiveness of bismuth shielding in reducing this exposure. TLDs were utilized to quantify the thyroid gland's radiation dose. One dosimeter was covered with a bismuth shield, while the other was left uncovered, thus protecting one lobe of the thyroid gland while leaving the other unprotected. The calculated radiation dose for the unprotected thyroid lobe was 24 mGy, whereas the dose for the protected lobe was measured at 17.50 mGy. This suggests that employing a bismuth shield can decrease the superficial radiation exposure to the thyroid gland by an estimated 43.95%.

Humans are exposed to natural background radiation daily from the earth, air, food, and cosmic rays. The majority of this background radiation comes from radon gas and its decay products. The average annual dose from natural background radiation worldwide is estimated to be between 1 and 10 mGy, with an average of approximately 2.4 mGy/year, half of which (1.2 mGy/year) is due to radon and its decay products [3]. However, due to the mixed nature of many radiation sources, the exact percentage of low LET natural background radiation is difficult to estimate.

Beyond the natural background radiation, human beings are subjected to artificial sources of radiation, encompassing the medical, research, and industrial applications of radioactive substances and X-ray equipment. A study conducted in 1987 found that 82% of the annual radiation exposure of the U.S. population was from natural background radiation, while 18% was from man-made sources [10]. Medical X-rays and nuclear medicine account for 79% of human-made radiation exposure, while consumer products (e.g., tobacco, building materials, televisions, and computer screens) account for 16%, and occupational exposure, nuclear explosions, and nuclear fuel cycles account for less than 5%.

Over the last ten years, the swift advancement in CT technology and its applications in the clinical field have contributed to a notable rise in both the frequency of CT scans and the extent of body area covered per scan. Presently, CT scans represent 5% of global radiological procedures and a third of the total medical radiation exposure [11]. The proliferation of CT usage is ongoing, now comprising 15% of all diagnostic processes and 75% of the cumulative diagnostic radiation dose in major healthcare facilities [12]. However, unlike other X-ray-based examinations, CT scan parameters vary widely in practical applications, even though they are generally the same for most patients [13].

Numerous methodologies have been formulated to minimize radiation exposure while ensuring the effective utilization of CT imaging, taking into account the clinical justifications, the patient's age or physique, and the specific region under examination. [14]. In 1993, the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) documented that an estimated 93 million CT scans were conducted globally each year. This translates to a rate of 16 scans per 1,000 individuals [3]. The advent of helical and multi-slice CT technologies has markedly elevated the application of CT in the fields of vascular, cardiac, and oncological imaging, consequently amplifying the associated radiation exposure [15].

Research has demonstrated that the application of bismuth shielding can significantly mitigate radiation exposure to superficial radiosensitive organs, notably the thyroid gland. Investigations have documented reductions in radiation doses that vary between 25% and 84%, influenced by variables including the type of scanner utilized and the configuration of the shielding [5]. However, bismuth shields can also introduce image noise and artifacts, which can be mitigated by using foam spacers to increase the distance between the shield and the organ, thereby maintaining acceptable image quality for diagnostic purposes [16].

In our study, the use of bismuth shielding reduced the radiation dose to the thyroid gland by approximately 43.95%. This outcome aligns with prior research, which has corroborated the efficacy of bismuth shields in diminishing radiation exposure to the thyroid [9]. However, it is important to note that the use of bismuth shields can also increase image noise, which can affect diagnostic accuracy.

In light of the increased risk for radiation-induced thyroid malignancies, it is imperative to minimize exposure to the thyroid gland during computed tomography (CT) scans. It is essential for patients to be thoroughly briefed on the necessity of the procedure as well as the potential immediate and long-term consequences of radiation exposure, allowing them to make an informed decision regarding their participation in the scan. The justification for MDCT must be rigorously evaluated, with a preference for alternative

diagnostic methods when feasible. Employing low-dose protocols is crucial to diminish the radiation dosage, and protective measures for superficial radiosensitive organs, including the thyroid, breasts, and gonads, should be implemented. Furthermore, it is vital to educate clinicians who refer patients for CT scans about the hazards associated with radiation exposure. Particular care should be taken with vulnerable patient populations, such as children and women younger than 40 years, to circumvent unnecessary scans whenever possible.

CONCLUSION

The findings of our research indicate that employing bismuth shielding substantially decreases the radiation exposure to the thyroid gland in neck MDCT scans. Nonetheless, it is imperative to meticulously address the resultant elevation in image noise and artifacts to preserve diagnostic precision. Additional studies are essential to refine shielding strategies and explore alternative approaches for reducing radiation exposure without compromising the quality of the images.

Ethical statement

This research received approval from the institutional ethics committee (Istanbul University Cerrahpaşa Medical Faculty, Decision no: 10254, date: 17.08.2006), and informed consent was obtained from all participants involved.

Data availability

The data sets produced and/or examined over the course of the present investigation can be obtained from the lead author upon a justified request.

Authors' Contribution

Study Conception: YB; Study Design: YB; Supervision: YB; Funding: N/A; Materials: YB; Data Collection and/or Processing: YB; Statistical Analysis and/or Data Interpretation: YB; Literature Review: YB; Manuscript Preparation: YB and Critical Review: YB.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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Identification of needs of family members of surgical intensive care unit patients: a cross-sectional study

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ABSTRACT

Objectives: It is aimed to determine the needs of family members whose patients are hospitalized in surgical intensive care unit.

Methods: Data were collected from 150 family members hospitalized in the surgical intensive care unit of a large university hospital. Data were collected using the Patient Relative Introduction Form and the Patient Relatives' Needs Scale in Intensive Care Units (CCFNI=Critical Care Family Need Inventory).

Results: Of the participants, 25.3% are female, while 68.7% are married. While 71.3% of the participants stated that they received information from their patients in the days following admission, only 4% of the participants were informed about intensive care; all participants stated that they were not given any pamphlets or brochures about intensive care. Among the healthcare professionals, doctors were identified as the individuals who establish solid and reliable communication, with 53% of the participants.

Conclusions: It has been determined that the needs of patient relatives are very important, with the most crucial need being to know the patient's chances of recovery. Meeting all the physical, mental, and psychosocial needs of patients and their relatives receiving treatment in intensive care units can only be achieved through assessments and taking necessary precautions. This approach aligns with a family-centered care approach and establishes a quality healthcare service infrastructure. This research provides data on patient experiences and the needs of patient relatives.

Keywords: Surgical intensive care, nursing care, family requirements, family members' needs

Intensive Care Units (ICU), where intensive treatment/care practices are provided to critically ill patients and are isolated areas, differ from other care settings in hospitals [1, 2]. Consequently, with the admission of a patient to the intensive care unit, different crises arise for the patient and their family [3]. Factors contributing to the emergence of crises include restricted interaction with the patient and family, the patient's critical condition and risk of mortality, changes in the family's routine life, increased need for information about the patient's health status, rules of the institution or ICU that family members must adhere to, and the family's financial difficulties [4]. Planning and providing care in the intensive care unit may lead to neglecting or overlooking details of the patient's condition, despite aiming to alleviate the physical and psychological stress experienced by the patient [5].

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The survival of the patient as a loved one, along with physical changes and adverse effects within the family, is noteworthy. Before the occurrence of family events, only a 1.2% rate of health problems was experienced, but after the patient's illness, this rate increased to 17.9%; common health issues frequently reported among family members include the onset of insomnia, changes in eating and drinking habits, and disturbances in bowel habits [6].

In Molter's study, "hope needs" were identified as universal components of the patient's relatives. In addition, other significant circumstances such as access to adequate and reliable information and the hospital staff's attitude towards patient information are given as consequential outcomes. Despite the provision of alternative resources for meeting family needs, patient families desire these services to be addressed by healthcare providers supported by physicians and nurses [7].

In other studies, the needs of family members during the intensive care period are ranked as information, trust, and closeness [8-10]. Family members express the desire to know that their loved ones are being well cared for and indicate that they want to receive information on this at least once a day [11].

There are studies conducted using different methods to determine the needs of patient families [4, 12-15]. Through identifying these needs, quality counseling and education will be provided to families based on their priority needs, ensuring continuity of nursing care and comprehensive care, assisting in reducing recurrent admissions, and preventing complications. It is believed that early detection will lead to an increase in the quality of life for intensive care patients and their families. However, in our country, especially in surgical intensive care, the number of studies aimed at determining the needs of patient families is limited [6, 13, 16]. The conducted studies mostly focus on general intensive care family needs. In this context, this study aims to determine the needs of family members of patients admitted to surgical intensive care.

METHODS

Population and Sample of the Research

This study is a descriptive and cross-sectional study. In the study, data on patients and family members who met the sampling criteria for Determination of Family Needs of Surgical Intensive Care Unit Patients were collected. Research data were collected after Ethics Committee approval (2021/037), approval of the institution where the research would be conducted, and consent of the volunteer family members.

Interviews were conducted with the relatives of the patients who volunteered to participate in the study by face-to-face interviews inside or outside the hospital.

Data Collection Forms and Explanations

Patient Relative Introduction Form

In the study, a 35-question form prepared by the researchers by reviewing the literature, including demographic characteristics, degree of closeness, duration of stay in surgical intensive care, number of hospitalizations in surgical intensive care, days of hospitalization in surgical intensive care, and questions about surgical intensive care and hospital was used [6, 13, 17].

Patient Relatives' Needs Scale in Intensive Care Units

In order to determine the needs of family members of patients hospitalized in the intensive care unit, the Critical Care Family Need Inventory (CCFNI=Critical Care Family Need Inventory) developed by Molter [7] in 1979 will be used. The scale was developed as a clinical tool to emphasize the importance of the needs of families with patients in intensive care and to measure family needs.

Reliability and validity studies have been conducted in many languages and cultures. A validity-reliability study was conducted by Büyükçoban *et al*. [13] to adapt the scale to the Turkish population. The Cronbach's alpha value of the original scale was found to be 0.93.

The NMMRS consists of 40 questions and is graded from 1 to 4 (1=Unimportant, 2=Slightly important, 3=Important, 4=Very important). There are five need sub-dimensions in the scale: "Trust", "Information", "Proximity", "Support", "Comfort". The questions belonging to the "Information" sub-dimension in the scale; 2-3-9-11-13-14-17-33-34, questions belonging to the "Trust" sub-dimension; 4-12-15-38-39, questions belonging to the "Proximity" sub-dimension; 8-26-32-35-36-37-40, questions belonging to the "Support" sub-dimension; 1-5-7-10-16-21-22-23-24-

Table 1. Information about the participants

	mean±SD	Median (min-max)
Age (year)	40.11±13.04	40 (18-69)
Patient's intensive care stay (days)	10.35±12.83	6 (1-77)
Time spent in hospital per day (hours)	5.52±3.26	5 (1-18)
	n	**%**
Gender		
Female	38	25.3
Male	112	74.7
Marital status		
Married	103	68.7
Single	47	31.3
Social health insurance		
Yes	106	70.7
No	44	29.3
Education status		
Literate	15	10.0
Primary education	23	15.3
High School	54	36.0
Bachelor's degree or higher	58	38.7
Occupation status		
Self-employment	36	24.0
Public employee	64	42.7
Housewife	9	6.0
Retired	12	8.0
Unemployed	29	19.3
Place of residence		
Province center	111	74.0
Village	8	5.3
District	17	11.3
In another province	14	9.3
Income status		
Income more than expenditure	15	10.0
Income equal to expenditure	60	40.0
Income less than expenditure	75	50.0
Relationship with your patient 1st degree relative		
Child	11	7.3
Wife	22	14.7
Mom and dad	65	43.3
Brother	30	20.0
2nd degree relative		
Uncle	7	4.7
Uncle	3	2.0
Still	2	1.3
Auntie	10	6.7
Place of accommodation for family members during the surgical intensive care unit		
Hospital garden	95	63.3
Own house	102	68.0
Hotel	11	7.3
Hospital canteen	10	6.7
Next of kin	30	20.0
Hospital waiting room	92	61.3
Relatives' homes	10	6.7
Where do you meet your basic needs such as eating and drinking? (You can select more than one option)		
Hospital canteen	105	70
Own home or a relative's home	121	80.7
Restaurant inside the hospital	35	23.3
Nearest restaurant	55	36.7

Min=minimum, Max=maximum, SD=standard deviation

27-28-30-31, questions belonging to the "Comfort" sub-dimension; 6-18-19-20-25-29 [13]. The relatives of the patients were asked to rate each item between 1-4 points, and each need expression in the scale was evaluated with "Unimportant" 1 point, "Less Important" 2 points, "Important" 3 points, and "Very Important" 4 points. In the scoring of the data, each need item is collected within the need sub-dimensions to which it belongs.

However, the "Trust, Information, Proximity, Support, Comfort" sub-dimensions of the scale are evaluated separately. Lower scale sub-dimension mean scores indicate that the needs are decreasing, while higher mean scores indicate that the needs are increasing. Permission for the use of the CCFNI was obtained from the author via e-mail.

Statistical Analysis

R vers. 2.15.3 program (R Core Team, 2013) was used. Minimum, maximum, mean, standard deviation, median, first quartile, third quartile, frequency and percentage were used to report the study data. The conformity of quantitative data to normal distribution was evaluated by Shapiro-Wilk test and graphical analysis. Independent groups t test was used in the evaluations of the variables showing normal distribution between two groups. Mann-Whitney U test was used in the evaluations of variables that did not show normal distribution between two groups, Kruskal-Wallis test and Dunn-Bonferroni test were used in the evaluations between more than two groups. Pearson correlation analysis was used to determine the level of relationship between quantitative data. Cronbach's alpha coefficient was used to determine the internal consistency of the scale items. Statistical significance was accepted as $P<0.05$.

RESULTS

The ages of the participants ranged between 18 and 69 years and the duration of the patients' stay in intensive care unit ranged between 1 and 77 days. The daily time spent by the patient's relatives in the hospital varied between 1 and 18 hours. While 25.3% of the participants were female; 68.7% were married. While 10% of the participants were literate, the rest were distributed as primary, high school and higher education; 24% were self-employed, 42.7% were public employees, 6% were housewives, 8% were retired, 19.3% were unemployed and only 10% of them had an income higher than their expenses. 26% of the partici-

Table 2. Table Family members' information and communication status with intensive care unit staff (N=150)

	n	%
Family members' access to information and communication with intensive care unit staff	**6**	**4**
Obtaining information about the patient's condition on the first day of admission		
Yes	**111**	**74**
Receiving information about the patient's condition in the following days		
Yes	**107**	**71.3**
Obtaining information about the intensive care environment on admission of the patient		
Yes	**6**	**4**
Getting information about the intensive care environment and procedures with a booklet/brochure		
Yes	**0**	**0**
Communicate with care and treatment providers		
Yes	**107**	**71.3**
Feeling in a decision-making role as a family member		
Yes	**55**	**36.7**

pants live far away from the hospital and 95 of them live in their own homes. 70% of the participants used the hospital canteen to meet their basic needs (Table 1).

While 71.3% of the participants stated that they received information from their patients in the days following hospitalization, only 4% of the participants were informed about intensive care and all of the participants stated that they were not given booklets or brochures about intensive care. 65.3% of the participants stated that the care of other family members was disrupted due to the needs and care of their relatives in intensive care, 56% stated that their responsibilities at home, 70.7% stated that their family relationships and 91.3% stated that their social life was affected. 57.3% of the participants stated that there was an increase in their current health problems; 71.3% stated that they could communicate with caregivers and treatment providers (Table 2).

When the distribution of healthcare professionals from whom family members received information about the condition of their patients was examined, it was determined that 64.7% and 56% of the healthcare professionals were doctors in the first and the following days after hospitalization, respectively; again, among the healthcare professionals, doctors were the ones with whom the participants established strong and reliable communication with 53% (Table 3).

The number of items, possible score ranges, minimum-maximum, medians, means, standard deviations and internal consistency values of the scale sub-dimensions of the Patient Relatives' Needs Scale in Intensive Care Units, which are comfort, closeness, trust, information and support, are given in Table 4.

There was no statistically significant difference

Table 3. Distribution of healthcare professionals from whom family members received information about the condition of their patients (n=150)

Health worker received information	n	%
Health worker received information on the first day of hospitalization		
Doctor	**97**	**64.7**
Nurse	**2**	**1.3**
Other health personnel	**12**	**8**
None	**39**	**26**
Health worker received information in the following days of hospitalization		
Doctor	**84**	**56**
Nurse	**7**	**4.7**
Other health personnel	**43**	**28.7**
None		
Healthcare worker receiving any information about the hospital and intensive care environment		
Doctor	**1**	**0.7**
Nurse	**1**	**0.7**
Other health personnel	**4**	**2.6**
None	**144**	**96**
Healthcare worker establishing a solid and reliable communication with the persons caring for and treating the patient		
Doctor	**80**	**53.3**
Nurse	**16**	**10.6**
Other health personnel	**4**	**2.7**
None	**50**	**33.4**

(P>0.05) between the total score and sub-dimensional scores of the CCFNI and the duration of daily stay in the hospital and gender of the participants. There was a statistically significant difference (P<0.05) between the total score and sub-dimensions of the CCFNI and the participants' age, length of stay in the intensive care unit, marital status, social security, occupation, proximity to the patient, place where basic needs are met - hospital canteen, presence of other dependent person, affecting home responsibilities, and history of health problems. It was determined that there was a statistically significant correlation only between the total score and sub-dimensions of the CCFNI and the participants' place of residence; support, comfort sub-dimensions and accommodation-hospital canteen; trust, CCFNI total score and restriction of social life; trust, closeness, CCFNI total score and affecting responsibilities at home; knowledge, trust, comfort, CCFNI total score (P<0.05) (Table 5).

It was found that there was a statistically significant positive correlation between the participants' CCFNI Knowledge scores and Trust (r=0.913, P<0.001), Proximity (r=0.827, P<0.001), Support (r=0.851, P<0.001), Comfort (r=0.812, P<0.001) sub-dimension and total (r=0.949, P<0.001) scores. It was found that there was a statistically significant positive relationship between the participants' CCFNI Trust scores and closeness (r=0.849, P<0.001), support (r=0.733, P<0.001), comfort (r=0.772, P<0.001) sub-dimension and total (r=0.886, P<0.001) scores. It was found that there was a statistically significant positive correlation between the participants' CCFNI Intimacy scores and Support (r=0.810, P<0.001), Comfort (r=0.812, P<0.001) sub-dimension and total (r=0.910, P<0.001) scores. It was found that there was a statistically significant positive relationship between the participants' CCFNI Support scores and Comfort (r=0.822, P<0.001) sub-dimension and total (r=0.950, P<0.001) scores. It was found that there was a statistically significant positive correlation between the participants' CCFNI Comfort scores and total (r=0.902, P<0.001) scores (Table 6).

DISCUSSION

Since the hospitalization of the patient in the intensive care unit is usually the result of an acute situation, a stressful and difficult process begins for the family members, for which they are not prepared and will face unknown things [18, 19]. They feel hopeless and helpless if there is no one to give them information and meet their needs. Therefore, it is necessary to know what family members need in order to successfully complete this process [20]. In recent years, many studies have been conducted to determine the concerns and needs of family members with patients in intensive care, and interventions to increase the well-being of both patients and family members have come to the agenda. In this context, it is generally recommended to improve communication, support systems and provide a relaxing/appropriate physical environment [20].

In a study conducted in our country to determine the needs of 201 relatives of patients with patients in the intensive care unit, it was found that seven of the 10 needs perceived as the most important by family

Table 4. Mean scores of the sub-dimension of the patient relatives' needs scale in intensive care units

Scale sub-dimensions	Number of items	Possible score range	Min-Max (Median)	Mean±SD	Internal consistency
Comfort	**6**	**6-24**	**12-24 (22)**	**21.05±2.88**	**0.900**
Closeness	7	7-28	18-28 (26)	25.13±2.97	0.861
Confidence	**5**	5-20	14-20 (19)	18.26±1.93	0.865
Information	**9**	9-36	21-36 (33)	31.22±4.59	0.919
Support	**13**	13-52	27-52 (41)	43.27±7.30	0.948
Total	**40**	40-160	97-160 (138.5)	138.93±18.30	0.977

Min=minimum, Max=maximum, SD=standard deviation

Table 5. Comparison of the participants' scores on the CCFNI according to their descriptive characteristics

Features		Information	Confidence	Closeness	Support	Comfort	CCFNI total score
Age	**r**	0.412	0.403	0.423	0.440	0.378	0.449
	P value	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***
Patient's length of stay in intensive care	**r**	0.212	0.163	0.179	0.149	0.057	0.168
	P value	**0.009***	**0.046***	**0.028***	**0.070**	**0.491**	**0.040***
Daily time spent in hospital	**r**	0.106	0.084	-0.002	-0.133	0.022	-0.014
	P value	**0.196**	**0.307**	**0.981**	**0.105**	**0.792**	**0.861**
Gender							
Female	38	31.58±4.82	18.21±2.12	25.18±3.16	44.32±6.49	20.92±3.06	140.21±18.31
Male	112	31.1±4.52	18.28±1.87	25.11±2.92	42.92±7.55	21.09±2.82	138.49±18.36
[a]Test value (t)		**0.557**	**-0.182**	**0.138**	**1.019**	**-0.311**	**0.499**
P value		**0.578**	**0.856**	**0.891**	**0.310**	**0.757**	**0.618**
Marital status							
Single	47	28.49±4.5	17.06±1.9	23.47±2.84	38.89±6.21	19.47±2.89	127.38±16.47
Married	103	32.47±4.07	18.81±1.69	25.88±2.73	45.27±6.9	21.77±2.58	144.19±16.66
[a]Test value (t)		**-5.366**	**-5.632**	**-4.965**	**-5.631**	**-4.875**	**-5.753**
P value		**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***
Social security							
There is	106	31.89±4.46	18.56±1.82	25.58±2.88	44.44±7.12	21.58±2.76	142.05±17.78
No	44	29.61±4.54	17.55±2.02	24.05±2.96	40.45±7.02	19.75±2.75	131.41±17.52
[a]Test value (t)		**2.828**	**2.999**	**2.941**	**3.136**	**3.706**	**3.351**
P value		**0.005***	**0.003***	**0.004***	**0.002***	**<0.001***	**0.001***
Profession							
Self-employment	36	29 (26, 35)	18 (16.5, 20)	24.5 (22, 28)	39.5 (36, 46)	20 (18, 24)	130 (119, 150)
Public employee	64	33 (27, 36)	19.5 (17, 20)	26 (24, 28)	42 (39, 52)	22 (18, 24)	140 (127, 160)
Housewife	9	36 (29, 36)	20 (16, 20)	28 (21, 28)	50 (39, 52)	24 (18, 24)	158 (122, 160)
Retired	12	36 (36, 36)	20 (20, 20)	28 (28, 28)	52 (51, 52)	24 (24, 24)	160 (159, 160)
Unemployed	29	29 (28, 34)	18 (16, 20)	24 (22, 26)	39 (36, 47)	19 (18, 23)	129 (119, 149)
[b]Test value (χ2)		**13.416**	**9.556**	**11.103**	**17.156**	**14.357**	**16.471**
P value		**0.009***	**0.049***	**0.025***	**0.002***	**0.006***	**0.002***
Place of residence							
Province center	111	33 (27, 36)	19 (17, 20)	26 (22, 28)	43 (38, 52)	22 (18, 24)	139 (123, 160)
Village	8	28 (26, 31.5)	18 (17.5, 19)	23 (22, 25.5)	34 (31, 41)	18 (17, 19.5)	119 (115, 133.5)
District	17	35 (28, 36)	19 (17, 20)	27 (24, 28)	41 (39, 52)	24 (19, 24)	148 (118, 160)
In another province	14	31.5 (28, 36)	19.5 (17, 20)	25.5 (23, 28)	40 (38, 51)	22 (18, 24)	134.5 (123, 158)
[b]Test value (χ2)		**3.677**	**0.346**	**3.592**	**9.375**	**11.988**	**7.206**
P value		**0.299**	**0.951**	**0.309**	**0.025***	**0.007***	**0.066**
Proximity							
First degree	128	33.5 (28, 36)	20 (17, 20)	26 (23, 28)	43.5 (39, 52)	22 (18, 24)	142 (124, 160)
Second degree	22	27 (25, 35)	16.5 (15, 19)	23 (21, 27)	38 (35, 51)	18.5 (18, 24)	120.5 (116, 156)
[c]Test value (z)		**-3.090**	**-3.372**	**-2.719**	**-2.373**	**-2.075**	**-2.805**
P value		**0.002***	**0.001***	**0.007***	**0.018***	**0.038***	**0.005***
Accommodation - Hospital canteen							
No.	140	33 (27, 36)	19 (17, 20)	26 (23, 28)	42 (38, 52)	22 (18, 24)	140.5 (123, 160)
Yes	10	28.5 (28, 29)	17 (15, 18)	22 (21, 24)	39 (34, 40)	18.5 (18, 24)	120 (119, 129)
[c]Test value (z)		**-0.809**	**-2.073**	**-1.963**	**-1.950**	**-1.370**	**-2.084**

Table 5 Contunied. Comparison of the participants' scores on the CCFNI according to their descriptive characteristics

P value		**0.419**	**0.038***	**0.051**	**0.051**	**0.171**	**0.037***
Where basic needs are met - Hospital canteen							
No	45	33.33±3.62	19.04±1.64	25.98±2.9	46.22±6.22	21.87±2.57	146.44±15.75
Yes	105	30.31±4.67	17.92±1.95	24.76±2.94	42.01±7.39	20.7±2.94	135.7±18.44
[a]Test value (t)		**4.275**	**3.618**	**2.328**	**3.348**	**2.319**	**3.630**
P value		**<0.001***	**<0.001***	**0.021***	**0.001***	**0.022***	**<0.001***
Presence of other dependent person							
Yes	103	32.2±4.21	18.77±1.65	26.08±2.35	44.55±7.33	21.66±2.72	143.26±16.9
No.		29.06±4.67	17.15±2.05	23.04±3.16	40.47±6.47	19.7±2.78	129.43±17.81
[a]Test value (t)	47	**4.090**	**4.750**	**5.883**	**3.437**	**4.064**	**4.573**
P value		**<0.001***	**<0.001***	**<0.001***	**0.001***	**<0.001***	**<0.001***
Influencing responsibilities at home							
Yes	84	34 (29, 36)	20 (17, 20)	27 (24, 28)	45 (39, 52)	22 (18, 24)	147.5 (124, 160)
No	12	27 (25.5, 31)	16 (15, 18.5)	21.5 (21, 23)	38 (36.5, 39)	18 (18, 19)	120.5 (116, 129.5)
Partially	54	29 (27, 36)	18 (17, 20)	25.5 (23, 28)	40 (38, 52)	22 (18, 24)	134.5 (123, 160)
[b]Test value (χ2)		**8.272**	**8.404**	**10.716**	**4.851**	**7.231**	**6.976**
P value		**0.016***	**0.015***	**0.005***	**0.088**	**0.027***	**0.031***
Social life constraints							
Yes	137	33 (28, 36)	20 (17, 20)	26 (23, 28)	41 (38, 52)	22 (18, 24)	140 (123, 160)
No.		27 (26, 35)	16 (15, 19)	21 (21, 27)	38 (36, 51)	18 (18, 24)	120 (116, 156)
[c]Test value (z)	13	**-1.881**	**-2.728**	**-2.742**	**-1.424**	**-2.010**	**-2.189**
P value		**0.060**	**0.006***	**0.006***	**0.154**	**0.044***	**0.029***
History of health problems							
Yes	89	31.88±4.54	18.55±1.8	25.75±2.75	44.92±6.97	21.6±2.78	142.7±17.73
No.	61	30.26±4.52	17.84±2.05	24.21±3.08	40.87±7.16	20.25±2.85	133.43±17.85
[a]Test value (t)		**2.143**	**2.258**	**3.209**	**3.460**	**2.892**	**3.137**
P value		**0.034***	**0.025***	**0.002***	**0.001***	**0.004***	**0.002***
Feeling decision-making about the patient							
Yes	55	32.6±4.28	18.75±1.82	26.09±2.58	44.45±8.15	21.89±2.86	143.78±18.4
No.	95	30.42±4.59	17.98±1.95	24.57±3.06	42.59±6.71	20.56±2.79	136.12±17.74
[a]Test value (t)		**2.872**	**2.381**	**3.107**	**1.438**	**2.797**	**2.516**
P value		**0.005***	**0.019***	**0.002***	**0.154**	**0.006***	**0.013***

r=Pearson correlation analysis

[a]Independent samples t test, results are presented as mean ± standard deviation.

[b]Cruskal-Wallis test, results are presented as median (first quartile, third quartile).

[c]Mann-Whitney U test, results are presented as median (first quartile, third quartile).

*P<0.05

Table 6. Levels of correlation between the scores of the CCFNI

		Information	Trust	Proximity	Support	Comfort	Total
Information	**r**	1.000					
	P value	-					
Trust	**r**	0.913	1.000				
	P value	**<0.001***	-				
Proximity	**r**	0.827	0.849	1.000			
	P value	**<0.001***	**<0.001***	-			
Support	**r**	0.851	0.733	0.810	1.000		
	P value	**<0.001***	**<0.001***	**<0.001***	-		
Comfort	**r**	0.812	0.772	0.812	0.822	1.000	
	P value	**<0.001***	**<0.001***	**<0.001***	**<0.001***	-	
Total	**r**	0.949	0.886	0.910	0.950	0.902	1.000
	P value	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	-

r=Pearson correlation analysis
*P<0.05

members were related to information, and the top three were the need to be informed about the patient's condition once a day, to make explanations in an understandable language and to inform the patient's home about changes in the patient's condition by telephone, followed by the need to "make sure that the patient is given the best care" and "to answer questions honestly" [20]. Similarly, in the study conducted by Sucu *et al*. [21] with 353 relatives of patients in order to determine the needs defined by family members with critically ill patients in the emergency department and the status of meeting these needs; it was found that nine of the ten most important needs were related to information; eight of the needs stated as important by the relatives of the patients were met by health professionals, although not one hundred percent, and these needs were mostly met by physicians.

Eroğlu *et al*. [22] conducted a study to determine the satisfaction levels of 152 patients and their relatives hospitalized in the intensive care unit of a university hospital and found that the relationship between nurses, patients and their relatives directly affected the patient's degree of well-being and satisfaction with the service provided. In addition to saving life and maintaining vital activities, supporting the patient and his/her family is among the main duties of the intensive care team [23, 24].

In the study conducted by Öztürk and Cerit [25], the average age of the patients' relatives was between 18 and 80, while in our study, the ages of the participants ranged between 18 and 69. In the same study, it was determined that 60% of the patients' relatives were female and 48% were primary and secondary school graduates; in the study conducted by Aykin [26], the ages of the patients' relatives ranged between 18 and 35 years and above, 54% of them were female and 28% were primary school graduates; in our study, 10% of the participants were literate, while the rest were distributed as primary, high school and higher education. In the study conducted by Boyraz [27], it was seen that the total scores of the needs were higher in those who graduated from primary school than those who graduated from higher education.

Accordingly, when the arithmetic score values of the sub-dimensions of the met needs inventory of the patients' relatives are analyzed, it is seen that the highest score is obtained from meeting the need for trust (2.55±0.54) and the lowest score is obtained from the sub-dimension of meeting the need for comfort (1.60±0.37) [25]. In our study, when the arithmetic score values of the sub-dimensions of the met needs inventory of the patient's relatives were examined, it was seen that they received the highest score from the sub-dimension of meeting the support needs (43.27±7.30) and the lowest score from the sub-dimension of meeting the trust needs (18.26±1.93).

In the study conducted by Öztürk and Cerit [25], 46% spent the night in hospital gardens, on benches, 54% spent the night in their homes because they wanted to be with the patient at all times, 91% wanted to have a place where they could spend the night nearby, while in our study, 26% of the participants lived far from the hospital and 95 of them stayed in their own homes.

In the study conducted by Aykin [26], it was observed that 65% of the patients' relatives stated that staying with the patient in the hospital affected their responsibilities at home, while 35% stated that it did not. 65.3% of the participants indicated that the care and needs of their relatives in the intensive care unit disrupted the care of other family members, and 56% stated that their household responsibilities; 70.7% mentioned their family relationships, and 91.3% mentioned their social life were affected. In a study by Öner *et al*. [28], 20% of the participants stated that being a companion next to the patient affected their work life, 4.6% mentioned their school life, 45.3% mentioned their family life, and 50% reported experiencing various health problems. In our study, 57.3% of the participants stated an increase in existing health problems.

CONCLUSION

It was found that the needs of patients' relatives are very important and the most important need is to know the patient's chance of recovery. Meeting all physical, psychological and psychosocial needs of patients and their relatives treated in intensive care units can only be achieved by making evaluations and taking necessary measures. This approach overlaps with the family-centered service approach and creates the infrastructure for quality health care. This study provides data on patient experiences and the needs of patient relatives. We recommend that similar studies be conducted as indicators of improvement and that institutional or individual efforts be made to address these problems identified in clinical settings.

Authors' Contribution

Study Conception: İÖ, AY, AK; Study Design: İÖ, AY, AK; Supervision: İÖ, AY, SK; Funding: İÖ, AY, SK, AK; Materials: İÖ, AY, SK; Data Collection and/or Processing: İÖ, AY, AK, SK; Statistical Analysis and/or Data Interpretation: İÖ, AY, AK; Literature Review: İÖ, AY, AK, SK; Manuscript Preparation: İÖ, AY, AK, SK and Critical Review: İÖ, AY, AK, SK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Comparative analysis of purse-string method versus conventional methods for stoma closure

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ABSTRACT

Objectives: Stoma surgery, essential for treating conditions like Crohn's disease, colorectal cancer, and diverticular disease, requires effective closure techniques to minimize postoperative complications and enhance patient outcomes. This study aims to compare the purse-string technique with traditional closure methods, emphasizing postoperative outcomes and complications.

Methods: This study retrospectively reviewed the medical records of 44 patients who underwent stoma closure at Antalya University Hospital between August 2015 and November 2019. Twenty-one patients underwent the purse-string (PS) method and twenty-three underwent conventional methods (CM). Patient demographics, such as age, sex, body mass index, and medical history, were recorded. Variables such as surgical duration, complication rates, and recovery periods were meticulously analyzed.

Results: The analysis indicated that patients treated with the PS method had notably reduced infection rates (9.5% in PS vs. 21.5% in CM) and quicker healing times compared to conventional methods. The circular suture pattern of the PS method demonstrated greater efficacy in minimizing postoperative complications. Complications were observed in 21.5% of patients with CM and 9.5% of patients with the PS method. Notably, systematic reviews have shown that the PS closure technique reduces surgical site infection (SSI) rates, although its impact on the length of hospital stay remains uncertain.

Conclusion: The PS method shows a significant advantage over traditional techniques in stoma closure. Its benefits in lowering infection rates and promoting quicker recovery emphasize its potential as a preferred method in surgical practice. The study advocates for the broader adoption of the PS method in clinical settings, given its positive impact on patient outcomes.

Keywords: Purse-string technique, conventional method, postoperative complications, stoma closure

A stoma is an artificial opening created in the abdominal wall as a surgical solution for various conditions, including colorectal cancer, inflammatory bowel disease, diverticular disease, and abdominal trauma. This allows the output of the colon (colostomy), ileum (ileostomy), or urinary tract (urostomy) to be collected in a bag. All surgical procedures that redirect the normal movement of bowel contents to the outside of the body when a portion of the bowel becomes diseased or is removed are referred to as stoma (ostomy) [1, 2]. Creating an ostomy involves bringing a part of the bowel through the ab-

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dominal wall, allowing waste to exit the body through this opening instead of passing through the anus [3]. The most common underlying conditions requiring stoma surgery are colorectal cancer, bladder cancer, ulcerative colitis, and Crohn's disease [4]. Another condition leading to stoma formation is inflammatory bowel disease, including colitis, ulcerative colitis, and Crohn's disease, which are the most frequent causes of ileostomy formation [5]. Although stoma formation is a straightforward intervention, its outcomes can be complex and potentially life-threatening. It is typically performed at the end of a lengthy and intricate surgical procedure [6].

Poorly performed stoma operations complications such as leakage, prolapse, parastomal hernia, and retraction may occur. The procedure can prolong patients' lives and help them return to a healthy life, but it can also cause various physiological, social, and psychological problems [7]. Individuals with a stoma frequently experience psychological challenges, including depression, anxiety, altered body image, low self-esteem, sexual difficulties, denial, loneliness, despair, and stigmatization [8]. Social issues may involve decreased interest in and participation in social activities, reluctance to travel, reduced work activity, and strained relationships [9, 10]. Closing stomas as quickly and efficiently as possible can positively impact patients' quality of life. Although stoma closure is considered minimally invasive, surgical site infection (SSI) is a common complication. SSI incidence following stoma closure ranges from 2% to 41%, primarily due to bacterial contamination of the skin around the stoma [11, 12]. The purse-string method (PS), introduced in 1997, reduces SSI risk and provides better cosmetic results [13]. Research on the effectiveness of PS is limited, but some studies suggest that placing a Penrose drainage tube under the subcutaneous tissue and using superficial incisions can help control SSI [1, 3].

This study aims to compare the purse-string method with conventional methods for stoma closure to determine the most effective and safe technique. By evaluating different surgical techniques and their impact on wound healing and complications after stoma closure, we can improve patient outcomes and enhance the quality of life for patients.

METHODS

The medical records of 44 patients who had their stomas closed were retrospectively reviewed. Between August 2015 and November 2019 at Akdeniz University Hospital, 21 patients who underwent the Purse-String (PS) method and 23 patients who underwent the Conventional Method (CM) were compared.

Purse-String (PS) Method Group

This group consisted of 21 patients who underwent stoma closure using the purse-string closure technique. This method involves creating a circular purse-string suture around the stoma site to minimize wound tension and reduce the risk of SSI.

Conventional Linear Closure (CM) Method Group

This group included 23 patients who underwent the conventional linear closure technique. This method typically involves making an elliptical incision around

Table 1. Centers for Disease Control and Prevention Guidelines for Diagnosis of Superficial Wound Infection

Characteristics of Superficial SSI (Surgical Site Infection)
1. Purulent drainage, with or without laboratory confirmation, from the superficial incision.
2. Organisms isolated from fluid or tissue obtained aseptically from the superficial incision.
3. At least one of the following signs or symptoms of infection: Pain or tenderness, localized swelling, redness or heat, and superficial incision is deliberately opened by the surgeon unless the culture is negative.
4. Diagnosis of superficial incision SSI by the surgeon or attending physician.

Superficial infection occurs within 30 days after the operation and involves only skin or subcutaneous tissue of the incision and includes at least one of the characteristics mentioned above, and the wound site infection is defined as surgical site infection.

the stoma site and closing the wound linearly, which is commonly used for stoma closure.

Medical charts were examined for patient demographics, including age, sex, body mass index, and medical history such as the presence of diabetes, chronic obstructive pulmonary disease, cardiovascular disease, liver dysfunction, alcohol consumption (categorized as normal, moderate, or non-drinker), smoking (within one year prior to surgery), medication records, American Society of Anesthesiologists (ASA) score, and preoperative blood values for both PS and CM groups. This study received approval from the Akdeniz University Ethics Committee (23.11.2019/963).

Patients were included in the study if they were between 18 and 80 years of age, underwent elective stoma closure surgery for benign or malignant conditions such as colorectal cancer or inflammatory bowel disease, and had no history of abdominal radiation or chemotherapy within six months before surgery. All patients provided written informed consent to participate in the study. Patients were excluded if they had severe comorbidities such as uncontrolled diabetes or end-stage renal disease, a history of recurrent incisional hernias, ongoing infections at the stoma site, were pregnant or breastfeeding, or had incomplete medical records.

A Wound Site Assessment Survey was administered to all patients after obtaining written informed consent. SSI was defined as the presence of cellulitis or purulent discharge, with or without a positive bacterial culture, within 30 days after surgery (based on the CAE 1992 Centers for Disease Control and Prevention definition) (Table 1). Surgical wounds were routinely observed and assessed by the surgical team and monitored until 30 days post-operation.

Surgical Technique

All patients received preoperative mechanical bowel preparation. Prophylactic antibiotics (Cefazolin, 1g/day) were administered after the induction of general anesthesia. The skin surrounding the sutured stoma was removed, maintaining a margin of approximately 3-5mm. The bowel routes leading to the stoma were extracted from the abdominal cavity, and the sutured stoma was dissected. A functional end-to-end anastomosis or Albert-Lembert anastomosis was then performed. The peritoneum and rectus fascia were closed using Vicryl 1.0. The open ileostomy/colostomy was sutured, and the wound was irrigated with 500 ml of saline. Antibiotics were administered for three days postoperatively.

Statistical Analysis

Data were analyzed using Pearson's Chi-square and Fisher's exact tests for categorical variables. Continuous variables are presented as median (range) values. The Mann- Whitney U test was used for statistical comparison between groups. A P value of <0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics software, version 2.0 (USA).

RESULTS

Patient characteristics such as gender, age, Body Mass Index, ASA Score, and preoperative comorbidities are summarized in Table 2. There was no significant difference between the PS and CM groups in terms of age, gender, body mass index, preoperative comorbidities, ASA scores, and operative blood values.

The perioperative factors and postoperative complications of the PS and CM groups are summarized in Table 3. Postoperative bleeding was observed in 1 patient (4.3%) in the CM group. Anastomotic leakage was not observed in either group. The overall complication rates did not differ significantly between the CM and PS groups (P=0.346). The median postoperative hospital stay was 5 days (range, 3–19 days) in the CM group and 6 days (range, 3–24 days) in the PS group. The median operation time for the CM group was 67 minutes (range, 34-213 minutes) and 54 minutes (range, 40-190 minutes) for the PS group; this difference was not statistically significant (P=0.387). The median blood loss was 18 ml (range, 0-130 mL) in the CM group and 22 ml (range, 0-130 ml) in the PS group (P=0.226). The median wound length in the PS group was 0.6 cm, significantly shorter than the CM group's 6 cm (P<0.001). Postoperative complications revealed that SSI was observed in 4 patients (17.3%) in the CM group, whereas no SSI was observed in the PS group. A significant difference was noted in the incidence of superficial incisional SSI between the PS and CM groups (P=0.054) (Table 3).

Table 2. Clinical and demographic characteristics of patients (n = 44)

Characteristics	CM (n = 23)	PS (n = 21)	P value
Male gender	16	15	0.738
Female gender	7	6	
Age (years)	58 (32-79)	65 (28-80)	0.285
Body mass index (kg/m^2)	22 (16-27)	22 (14-29)	0.976
ASA score 1	4	5	
ASA score 2	19	15	
ASA score 3	0	1	
Preoperative comorbidities			
Diabetes	1	0	
Cardiovascular disease	4	5	
COPD	1	0	
Alcohol consumption	7	10	0.263
Smoking	6	7	0.836
Ileostomy/ colostomy	19/4	18/3	

All continuous variables are expressed as median (range). CM=conventional skin closure, PS=purse-string method for skin closure, ASA=American Society of Anesthesiologists, COPD=chronic obstructive pulmonary disease.

DISCUSSION

Intestinal stomas involve surgically bringing a portion of the small or large intestine through the anterior abdominal wall. While the fundamental principles of stoma formation are typically the same, various configurations are used for different indications. A diverting stoma prevents fecal flow from reaching the distal intestine to treat or prevent anastomotic leakage and is necessary in cases of sacral or perineal infections at risk due to constant fecal contact [14]. Permanent stomas are required when pathological anatomy prevents the restoration of gastrointestinal continuity, when patient comorbidities prohibit further surgery, or when re-anastomosis would adversely affect the quality of life [15]. The optimal skin closure technique following loop ileostomy reversal in stoma surgery has not yet been established [16].

Our study found that the PS technique significantly reduces SSI and provides better cosmetic results

Table 3. Perioperative factors in skin closure with Conventional Method (CM) and Purse String (PS).

Factors	CM (n=23)	PS (n=21)	P value
Operation time (min)	67 (34-213)	54 (40-190)	0.387
Blood loss (mL)	18 (0-130)	22 (0-130)	0.226
Wound length (cm)	6 (4-8)	0.6 (0.5-1)	**<0.001**
Complications	5	2	0.346
Wound infection	4	0	0.054
Anastomotic leakage	0	0	-
Postoperative bleeding	1	0	-
Postoperative hospital stay (days)	5 (3–19)	6 (3–24)	0.176

compared to conventional methods. There was no significant difference in operation time, length of hospital stay, or wound healing time between the groups. This finding is consistent with previous studies showing similar operation times and recovery periods for different stoma closure techniques. Patient characteristics, such as age, gender, body mass index, preoperative comorbidities, AS scores, and operative blood values, were comparable between the PS and CM groups, indicating that differences in outcomes are likely due to the closure techniques rather than patient demographics. Our findings align with Pokorny *et al*. [17], who reported similar complication rates, with 3% mortality, 20% wound infection, 10% bowel obstruction, and 5% anastomotic leakage. Similarly, Song *et al*. [18] reported a 32.7% complication rate in 55 patients after ileostomy reversal, including wound infection (24.3%), small bowel obstruction (16.4%), and incisional hernia (7.9%).

Kim *et al*. [19] found a 19.7% complication rate in 164 patients. Our study observed complications in 21.5% of patients with CM and 9.5% of patients with PS, supporting the evidence that the PS method results in fewer complications. The treatment of SSIs requires wound drainage, regular wound care, and sometimes antibiotics. However, cosmetic outcomes are often unsatisfactory, and the healing period is extended. Atallah *et al*. [20] reported better cosmetic outcomes with the PS technique, which our study corroborates.

Reid *et al*. [21] conducted a randomized clinical study comparing the PS method with conventional closure, finding a significantly lower infection rate for the PS group (0%) compared to the control group (36.6%). The healing time was also shorter in the PS group (3.8 weeks) compared to the conventional group (5.9 weeks). Patient satisfaction was higher in the PS group (70%) compared to the other group (20%) [21]. These findings are consistent with our results, where the PS group showed a significantly shorter wound length and fewer SSIs.

In a systematic review by Li *et al*. [22], the PS method was found to be the best skin closure technique in terms of reducing SSI after stoma reversal. Conventional techniques may lead to higher SSI rates due to inadequate drainage of subcutaneous exudate, increasing the risk of wound separation, incisional hernia, prolonged hospital stay, and higher healthcare costs. Additionally, delayed wound healing, unsightly scar formation, and poor cosmetic results are more likely in the conventional group [23].

Our study found a median wound length of 0.6 cm in the PS group compared to 6 cm in the CM group ($P<0.001$), indicating significantly better cosmetic outcomes with the PS technique. The incidence of superficial SSI was also lower in the PS group (0%) compared to the CM group (17.3%) ($P=0.054$), supporting the superiority of the PS method in preventing infections.

In summary, the PS method demonstrates significant advantages over conventional methods in reducing SSIs, improving cosmetic outcomes, and enhancing patient satisfaction. Further long-term studies are needed to confirm these benefits and establish the most effective closure technique for stoma reversal.

Limitations

There are some limitations in our study. Our study was planned retrospectively and the number of patients was limited. New studies with larger patient groups are needed. Thus, more risk factor analyses could be performed.

CONCLUSION

Our research results indicate that the purse-string technique results in significantly fewer surgical site infections and improved cosmetic outcomes compared to the conventional technique. Further studies with long-term follow-up are needed to confirm the potential benefits of the purse-string technique in reducing incisional hernias and improving cost-effectiveness. Surgical site infections present a substantial economic burden due to prolonged hospital stays, medication treatments, and increased overall treatment costs. The higher rate of surgical site infections in the conventional group may contribute to higher medical expenses. Additional costs associated with healthcare personnel providing continuous wound care in the conventional group should also be considered.

Ethical statement

This study received approval from the Akdeniz University Medical Faculty Clinical Research Ethics Committee (Decision date: 23.11.2019 and number:963).

Authors' Contribution

Study Conception: AH; Study Design: VV; Supervision: VV; Funding: N/A; Materials: N/A; Data Collection and/or Processing: AH; Statistical Analysis and/or Data Interpretation: AH; Literature Review: AH, VV; Manuscript Preparation: AH and Critical Review: AH, VV.

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Myotonia may be a sign that prompts genetic testing for myotonic dystrophy type 1

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ABSTRACT

Objectives: Myotonic dystrophy type 1 (DM1) is an autosomal dominant disorder characterized by myotonia, atrophy, and muscle weakness. Even though myotonic discharges can be shown on electromyography in DM1 instances, it is still difficult to distinguish DM1 clinically from other myotonic disorders. We aimed to examine the relationship between DM1 and myotonia.

Methods: Data from 22 patients who had myotonia were analyzed retrospectively. Patients with DM1 (n=9) and non-DM1 myotonia (n=13) were categorized by genetic testing.

Results: There was a significant difference in the incidence rates of myotonia (P=0.0001) between 8 out of 9 DM1 patients (89%) and 1 out of 13 non-DM1 (8%). Myotonic discharges were seen in 7 of the 9 DM1 (78%) patients. On the other hand, only 2 out of 13 (15%) patients with non-DM1 had myotonic discharges. There was a statistically significant difference in the incidence rates across the groups (P=0.003). In this study, we also encountered three siblings with DM1. We observed myotonia and muscle weakness in the twins, indicating there is a possibility of anticipation being seen in their grandchildren in the future.

Conclusion: Genetic counseling is crucial for understanding disease variability, aiding in better DM1 management.

Keywords: Myotonic dystrophy type 1 (DM1), DM1 protein kinase gene, myotonia, CTG repeats

Myotonic dystrophy type 1 (DM1) is an autosomal dominant disorder characterized by myotonia, atrophy, and muscle weakness [1]. An increase in CTG causes this condition repeats in the 3′ untranslated region (3′UTR) of the DM1 Protein Kinase (DMPK) gene. This microsatellite typically has 5-37 repeats, but at 50 repetitions or more, it becomes pathogenic because the enlarged CUG repeats (CUGexp) generate ribonuclear foci, which make the resultant RNA poisonous. RNA-binding proteins are bound and sequestered by hairpin structures seen in these foci [2]. DM1 patients frequently have myotonia, which is defined as having trouble releasing a contracted muscle [3, 4].

Myotonia is a unique electrodiagnostic result that is seen during the needle section of an electromyography (EMG) investigation. The structure and sound of EMG myotonia are distinctive, and when the recording needle is introduced into a muscle that is at rest, the usual dive bombardment sound is audible

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rather than electrical silence [5, 6]. In both the upper and lower extremities, myotonia is evident in the proximal and distal muscle groups [7]. Myotonia is a disease-specific clinical and electrodiagnostic indication that arises from skeletal muscle chloride channel failure [8]. Myotonia is associated with myotonic discharges on EMG. Myotonic discharges are easily recognized on electrodiagnostic testing because of the waxing and waning discharges [7].

Myotonic dystrophy is now classified as type 1 DM1 for the classic form and type 2 DM2 for the more recently discovered variation. Myotonia (present in 90% of affected individuals) and muscle dysfunction (weakness, pain, and stiffness) account for 82% of the symptoms of myotonic dystrophy type 2 DM2. Less frequently occurring conditions include subcapsular cataracts, cardiac conduction defects, and insulin-insensitive type 2 diabetes mellitus. While myotonia has been documented in the first ten years of life, it usually manifests in the third decade, usually with episodic or fluctuating excruciating muscular pain and weakening of the flexors in the neck and fingers. Rarely does myotonia result in severe symptoms [9]. DM2 is the sole additional hereditary form of multisystem myotonic dystrophy that has been discovered thus far. DM2 is caused by pathogenic polymorphisms in CNBP. CNBP intron 1 may include a complex repeat motif, (TG)n(TCTG)n(CCTG)n. DM2 is brought on by the CCTG repetition expanding. Counting the CTG repeats in myotonic dystrophy protein kinase (DMPK) allows one to distinguish between DM1, DM2, and other hereditary myopathies. To rule out other causes of muscle disease, further testing with EMG, serum CK levels, and/or muscle biopsy is frequently necessary if the DMPK CTG repeat length is within the normal range and DM2 has been ruled out by molecular genetic testing of CNBP.

During both meiosis and mitosis, the mutant DMPK CTG is unstable. Somatic mosaicism frequently results from the instability during mitosis. The afflicted people may exhibit mutations with varying sizes within a single tissue type or mutations with varying sizes across many tissue types. The patient population's diverse spectrum of clinical characteristics might perhaps be attributed to somatic mosaicism arising from mitotic instability [10, 11]. In the meanwhile, during the allele's transmission to the following generation, meiotic instability may cause changes in the CTG's size. In most cases, the size will increase, leading to more severe clinical symptoms known as anticipation and an earlier age of start. An individual with severe, early-onset diabetes usually gets the enlarged mutant allele from the mother [12, 13].

Our study aimed to investigate the relationship between myotonia in patients with DM1 by retrospectively analyzing their genetic report. Additionally, we sought to highlight the importance of genetic counseling for patients with myotonic dystrophy and their family members.

METHODS

We examined patients treated at Umraniye Training and Research Hospital from 2020 to 2024 for electrodiagnostic testing. Cases having verified gene test findings and myotonic discharges on the EMG were chosen. The research excluded patients who were on cholinesterase inhibitors or any other drug that might reduce myotonic discharges. The results of gene tests were used to divide the patients into two groups: the DM1 group and the non-DM1 myotonia group. Patients in the DM1 group had amplifications of the DMPK gene including more than 50 CTG trinucleotide sequence repeats. Patients without DM1 validated by gene testing made up the non-DM1 myotonia group. Both percussion and requesting the patient to carry out bodily actions like opening their eyes or squeezing their hand were used to demonstrate clinical myotonia.

Peripheral blood samples were taken after written consent was obtained from the patients. Genomic DNA was extracted from EDTA-anticoagulated peripheral blood using standard methods. DNA extraction from the blood sample was performed using a semi-automatic robot as recommended by the manufacturer (Qiagen). Concentration and quality control of DNA samples (260/280 nm and 260/230 nm values) were determined by fluorometric (Qubit v3.0) and UV spectrophotometry. We brought the reagents to room temperature. Vortex Primer Mix and PCR Mix were then spun briefly to remove debris from the cover. We mixed the enzyme gently by inverting or pipetting. Following the recipe given above, we prepared a Master Mix that calculates the number of samples and controls. We mixed briefly by pipetting or Vortex Master

Mix. For each sample, we transferred 21.5 µL of Master Mix into each 0.2 ml PCR tube. We added 1 sample of DNA (1-5 ng per reaction) to each PCR tube. We prepared a positive control PCR tube using the DNA provided in the kit and added 1 µl of sterile Direct Q dd H2O instead of DNA for the negative control. We vortexed each PCR tube. We made sure that no drops remained on the tube wall or lid. We placed the tubes in the thermal cycler. We used the following PCR program for amplification of all markers. The PCR products were incubated for three minutes at −20°C on ice or in a cold box. We centrifuged the plate for 10 seconds at 1000xg to get bubbles out of the wells. We placed the plate in the Genetic Analyzer and started the run. Samples were analyzed using Applied Biosystems® fragment analysis software compatible with the Genetic Analyzer for GT DM1 Detector. The program of PCR reaction was designed as follows: Initial Denaturation, 95°C 5 min; Denaturation, 95°C 1 min; Primer Annealing, 63°C 70 sec; Extension, 72°C 80 sec; Final Extension, 72°C 10 min; 30 cycles.

Statistical Analysis

The two-sample Pearson's chi-square test was used to assess the myotonia occurrence rate between the myotonic DM1 and non-DM1 groups. The statistical analyses were performed using SPSS version 21 at a significance level of $P<0.05$. Patients in the second group did not have DM1 validated by gene testing.

RESULTS

Individuals were divided into the DM1 and non-DM1 groups after being analyzed using Applied Biosystems® fragment analysis software compatible with the Genetic Analyzer for GT DM1 Detector (Fig. 1).

Following gender and age-based case matching

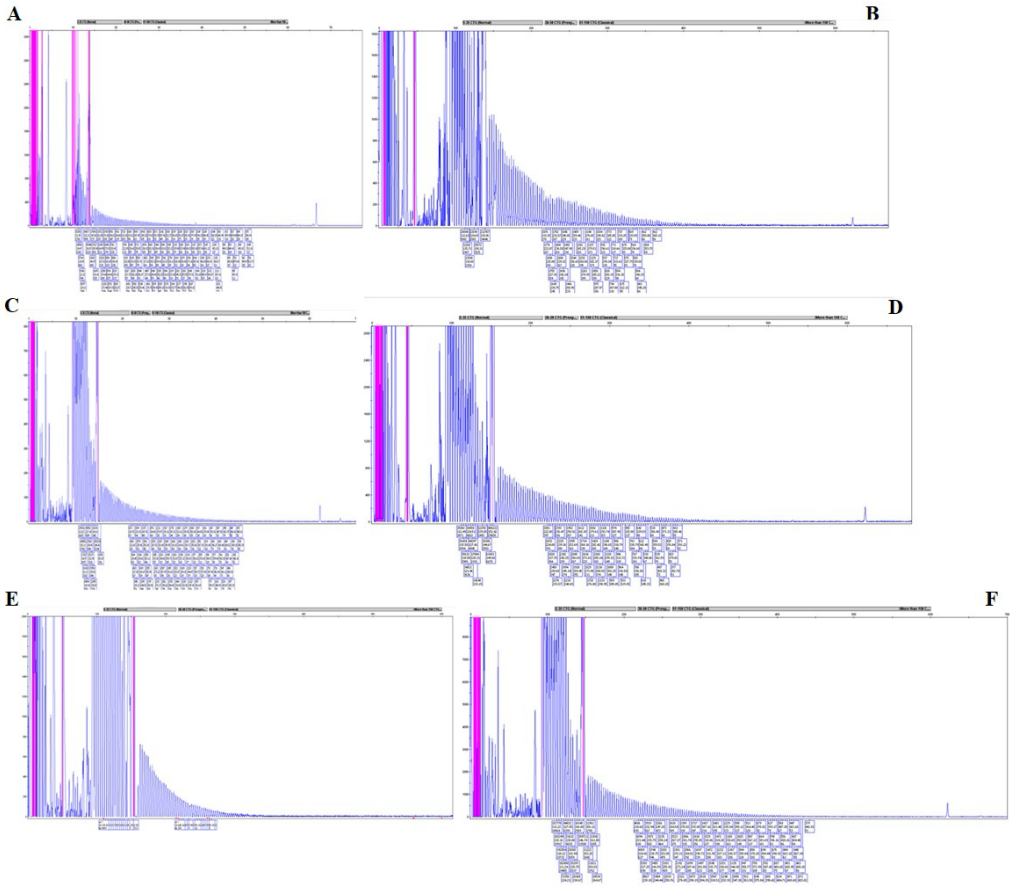

Fig. 1. DMPK gene 3'UTR region CTG repeat MLPA fragment analysis images. MLPA fragment analysis images of DM1 cases are shown here (A-F). The CTG repeat was over 50, and it has been genetically proven that the diagnosis is DM 1. MLPA=multiplex ligation-dependent probe amplification, DM1=muscular dystrophy type 1.

Table 1. **Clinical features of the patients**

No	Age/Sex	Eyes/Heart/ Gastrointestinal/Biliary tract/Genitourinary	Hair	Muscle/Soft tissue	Neurologic	Gene Transcript	The number of repetitions
1	39/F	No/ Not available		Myotonia, Myotonic discharge, Muscle weakness		NM_004409.5	**9/>50**
2	56/M	No/ Not available	Frontal balding	Myotonia, Myotonic discharge, Muscle weakness		NM_004409.5	**7/>182**
3	35/M	No/ Not available		Muscle weakness		NM_004409.5	**12/>111**
4	19/M	No/ Not available		Myotonia, Myotonic discharge, Muscle weakness	Speech disability	NM_004409.5	**16/>72**
5	39/M	No/ Not available		Mild muscle weakness		NM_004409.5	13/15
6	33/F	No/ Not available	Frontal balding	Mild muscle weakness		NM_004409.5	7/13
7	33/F	No/ Not available	Frontal balding	Mild muscle weakness		NM_004409.5	7/7
8	58/F	No/ Not available		Mild Muscle Weakness		NM_004409.5	7/7
9	52/M	No/ Not available		Myotonic discharge, Muscle weakness		NM_004409.5	7/21
10	14/M	No/ Not available		Mild muscle weakness		NM_004409.5	7/13
11	15/F	No/ Not available		Myotonic discharge, Muscle weakness		NM_004409.5	12/14
12	4/M	No/ Not available		Mild muscle weakness		NM_004409.5	11/14
13	43/F	No/ Not available		Myotonia, Muscle weakness		NM_004409.5	**14/>50**
14	42/F	No/ Not available		Myotonia		NM_004409.5	13/13
15	30/F	No/ Not available		Myotonia, Muscle weakness		NM_004409.5	**15/>50**
16	19/F	No/ Not available		Myotonia, Muscle weakness	Speech disability	NM_004409.5	**13/>50**
17	29/F	No/ Not available		Mild muscle weakness		NM_004409.5	4/22
18	26/F	No/ Not available		Mild muscle weakness		NM_004409.5	12/20
19	19/F	No/ Not available		Myotonia, Myotonic discharge, Muscle weakness		NM_004409.5	**13/>50**
20	12/F	No/ Not available		Mild Muscle Weakness		NM_004409.5	13/13
21	39/F	No/ Not available		Myotonia, Myotonic discharge		NM_004409.5	**10/>50**
22	51/F	No/ Not available		Mild muscle weakness		NM_004409.5	4/21

between the two groups, a total of 22 people were included in the study. Table 1 displays clinical symptoms, EMG readings, and gene test findings. Nine patients with mean age of 33.22±12.76 years comprised the DM1 group. They were all myotonic. This non-DM1 myotonia group consisted of thirteen patients with mean age of 31.38±16.89 years. Age and gender did not significantly differ across the groups (P=0.360 and P=0.899, respectively).

Seven of the nine patients in the DM1 group, or almost 78% of the total, had myotonic discharge. Myotonic discharge was seen in one patient out of the 13 in the non-DM1 myotonia group, representing an incidence rate of around 8%. There were notable variations in occurrence rates between the DM1 and non-DM1 myotonia groups (χ^2=8.56, P=0.003). Furthermore, there was a significant difference in the incidence rates of myotonia (P=0.0001) between 8 out of 9 DM1 patients (89%) and 1 out of 13 non-DM1 myotonia patients (8%).

In one household, we found three siblings. The younger sister, case 20, had a normal number of repetitions (13/13). Cases 19 and 16 are twin sisters, with DMPK 3'UTR CTG repeat counts of 13/>50. The mother of this family likewise had identical clinical signs but passed away, thus genetic testing could not be performed. The father was taken at an outside facility and genetic testing was verbally reported as normal.

DISCUSSION

We discovered a link between DM1 and myotonia. DM1 was significantly correlated with myotonia in the present research. This aligned with the findings of earlier investigations. Research revealed that distal motor weakness and related clinical and electrical myotonia are common in DM 1 patients [14, 15]. Myotonia might be a sign or symptom that leads people to inquire about genetic testing.

Moreover, we encountered three siblings including two twin patients in this study. The fact that their mother had the same symptoms and died at a young age suggests myotonic dystrophy, even if there is no opportunity for genetic testing. In addition, the fact that her father's genetic test was normal strengthens the possibility. We observed that muscle weakness and myotonia were prominent in the twin sisters. This is evidence of anticipation and demonstrates the necessity of genetic counseling for patients and family members. Genetic counseling provides critical information for family planning. Understanding the risks of passing on an expanded allele can help prospective parents make informed decisions. For instance, they might consider preimplantation genetic diagnosis or other reproductive options to reduce the risk of having a child with severe DM1 [16]. Counseling helps families understand the potential variability in disease presentation and progression due to genetic instability. This knowledge is crucial for preparing for the care needs of affected individuals and setting realistic expectations regarding the disease's impact on quality of life.

Because of the incredibly low incidence rate, this study's limited sample size is one of its limitations. In the future, larger sensitivity and specificity investigations will be required to validate these results. Moreover, our study examined the CTG repeat in the 3' UTR using classical PCR. However, while classical PCR can confirm whether the CTG repeat is over 50 or not, it is difficult to determine whether the CTG repeat is between 100-1000 or even over 1000, that is, it is difficult to decide which of the mild, classical and congenital subtypes it is. For this reason, it is necessary to use the Southern blotting. As we all know, having a Southern blotting device in every laboratory is impossible. For this reason, we are also unable to test the subtypes of DM1 in our study. We were unable to perform Southern blotting and prove that the patients' CTG repeat count was over 100.

CONCLUSION

Our study confirms that myotonia may be an important sign of DM1 associated with DMPK gene mutations. The strong correlation between DM1 and myotonia and the anticipation observed in familial cases emphasize the importance of genetic counseling. This counseling is crucial for family planning and understanding disease variability, aiding in better preparation and management of DM1's impact on quality of life.

Ethics Committee Approval

The participants have already given informed consent. This study was approved by the Ethical Committee of Umraniye Training and Research Hospital

(Ethics No: B.10.1.TKH.4.34. H.GP.0.01/143, 16/05/2024), School of Medicine, University of Health Sciences, Istanbul, Turkey.

Authors' Contribution

Study Conception: ME, GH, BK; Study Design: ME; Supervision: ME, GH; Funding: N/A; Materials: ME, BK; Data Collection and/or Processing: ME, BK; Statistical Analysis and/or Data Interpretation: ME, GH, BK; Literature Review: ME, GH; Manuscript Preparation: GH and Critical Review: ME, GH, BK.

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Increasing cumulative cabergoline dose in patients with prolactinoma improves metabolic parameters independently of decrease in prolactin levels

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ABSTRACT

Objectives: In prolactinoma patients treated with cabergoline, all of whom achieved normoprolactinemia, longitudinal changes in metabolic parameters and the factors influencing these changes were investigated.

Methods: This retrospective-longitudinal study was conducted at a pituitary disease center. Medical records of newly diagnosed prolactinoma patients between 2013 and 2023 were reviewed. After applying exclusion criteria, 102 prolactinoma patients were included in the final analysis. Clinical and laboratory parameters of prolactinoma patients were recorded. Metabolic parameters assessed were fasting plasma glucose, lipid levels, fasting insulin levels, HbA1c levels, and Homeostatic Model Assessment-Insulin Resistance (HOMA-IR) levels. Subsequently, metabolic parameters assessed at the initial and final visits were compared, and factors influencing these parameters were analyzed.

Results: All prolactinoma patients were treated with cabergoline, and all were in remission at their final visit. The treatment significantly reduced fasting plasma glucose, HbA1c, and LDL cholesterol levels ($P<0.05$). Although there were improvements in other lipid parameters, fasting insulin, BMI, and HOMA-IR compared to baseline, the differences were not statistically significant. A correlation analysis was conducted to identify factors influencing fasting plasma glucose, HbA1c, and LDL cholesterol levels at the final visit in prolactinoma patients. The analysis revealed that only the cumulative dose of cabergoline significantly impacted all three metabolic parameters ($P<0.05$).

Conclusions: Cabergoline not only balances prolactin levels but also directly improves metabolic health. Current and future evidence clearly indicates that dopamine agonists like cabergoline could be an effective treatment not only for patients with prolactinomas but also for individuals affected by metabolic disorders without hyperprolactinemia.

Keywords: Cabergoline, prolactinoma, glucose profile, lipid profile, metabolism

Prolactinomas are the most common pituitary tumors [1]. A high amount of secreted prolactin leads to well-known effects such as gonadal dysfunction and galactorrhea [2]. However, it also leads to many systemic disorders. One of these is its effect on metabolism. Recently, some negative effects

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of hyperprolactinemia on glucose and lipid metabolism have been demonstrated [3]. Furthermore, normalizing prolactin levels through treatment can bring back metabolic disturbances in patients with prolactinoma [4]. Previous studies have reported hyperglycemia, hyperlipidemia, and increased BMI in patients with prolactinoma. Dopamine agonists, particularly cabergoline, one of the primary treatments for prolactinoma, have been shown to have beneficial effects on these metabolic disturbances [3-5]. This metabolic restoration is attributed to prolactin's normalization, gonadal functions' improvement, and the positive metabolic effects of the dopamine agonists used for treatment [5]. Observing the change in metabolic parameters of prolactinoma patients reveals that both the hormone prolactin and the dopamine agonists, which inhibit the release of this hormone in metabolism, will make an essential contribution to our understanding. This study focused on the longitudinal changes in metabolic parameters in a group of prolactinoma patients treated with cabergoline, all of whom achieved normoprolactinemia. Factors influencing the altered metabolic parameters were also investigated.

METHODS

Study Design and Patients

The study adhered to the ethical principles for medical research involving human participants described in the World Medical Association's Declaration of Helsinki. The Ethics Committee of Istanbul University-Cerrahpasa approved the study (Approval Number: 16.10.2023-711105). This retrospective-longitudinal study was conducted at a pituitary disease center. Medical records of patients newly diagnosed with prolactinoma were reviewed between January 2013 and January 2023. The inclusion criteria were: i) adult patients over 18 years of age, ii) patients clearly diagnosed with prolactinoma based on guidelines [6], iii) patients treated with cabergoline, and iv) patients regularly followed up for at least six months. The exclusion criteria were: i) patients with hyperprolactinemia due to causes other than prolactinoma [7], ii) patients followed without treatment (those whose treatment was completed or those in a drug holiday), iii) patients treated with bromocriptine, iv) patients treated with surgery or radiotherapy, v) patients with incomplete metabolic evaluations at diagnosis and during follow-up, vi) patients receiving medical treatment for diabetes, hyperlipidemia, or obesity, vii) patients with hypopituitarism (however, patients with gonadal dysfunction at diagnosis whose gonadal function improved with cabergoline treatment were included), and viii) patients with insufficient follow-up duration.

The medical follow-up records obtained the patients' clinical and laboratory data and medication use. Data on medication use, duration, dosage, and intervals were reviewed from a government digital database (https://medeczane.sgk.gov.tr/doktor/login.jsp), which provides information on the history of prescribed medications.

Metabolic parameters evaluated at the initial and final visits were then compared, and factors influencing these metabolic parameters were analyzed.

Patient Management and Definitions

Medical therapy with dopamine agonists (DAs) was recommended as the initial treatment approach for patients diagnosed with prolactinoma. Cabergoline was initiated at 0.25-0.5 mg per week, and the DA dose was gradually increased until prolactin levels normalized. In this study, remission was defined as patients in whom symptoms had resolved, tumor progression was absent, and prolactin levels were below 20 ng/mL. Remission status was monitored every six months by evaluating symptoms and measuring prolactin levels.

Collected Data

The following parameters were examined in prolactinoma patients: age, sex, height, weight, body mass index (BMI), presenting symptoms, disease duration, duration of cabergoline use, cumulative cabergoline doses, comorbid conditions, and data on other medications. At the time of diagnosis and the final visits, the following were recorded: pituitary adenoma size, prolactin levels, anterior pituitary hormone levels, fasting plasma glucose, lipid levels, fasting insulin levels, and HbA1c levels. Homeostatic Model Assessment-Insulin Resistance (HOMA-IR) levels were calculated using the formula: fasting plasma glucose (FPG) (mg/dL) × fasting insulin (μU\mL) / 405 [8].

Biochemical Assays

Fasting blood samples were collected between 8:00 and 9:00 AM. Prolactin levels were measured using an electrochemiluminescence immunoassay (ECLIA). FPG, insulin, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides were measured using enzymatic colorimetric or immunoturbidimetric methods on Roche/Hitachi Cobas c systems.

Radiological Evaluation

High-resolution magnetic resonance imaging (MRI) of the pituitary gland and hypothalamic region was performed on all patients. Images were obtained using 1.5 Tesla MRI machines until 2018, after which a 3 Tesla MRI machine was used. The presence of a hypointense lesion following the intravenous injection of gadolinium indicated a pituitary adenoma. Lateral-lateral, dorsoventral, and craniocaudal diameters were measured, and the largest adenoma diameter was used for analyses.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 27.0). The data were first analyzed for normality using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation (SD) and median (interquartile range [IQR]). Student's t-tests or analysis of variance (ANOVA) were used to compare means between groups with a normal data distribution. Medians were compared using the Mann-Whitney U test and the Kruskal-Wallis test. Spearman's rank and Pearson correlation tests were employed to calculate correlation coefficients between continuous variables. Frequencies were compared using Pearson's chi-square test and Fisher's exact test. A paired-sample t-test was used to determine whether the baseline metabolic parameters differed from the final visit values. Results were analyzed with a 95% confidence interval, and a P-value < 0.05 was considered statistically significant.

RESULTS

Characteristics of Patients

The records of 328 newly diagnosed prolactinoma patients were reviewed. After applying the exclusion criteria, 102 patients were included in the final analysis. Table 1 presents the general characteristics of the patients.

Changes in Metabolic Parameters During Treatment

The changes in metabolic parameters evaluated at the time of diagnosis and the final visit in prolactinoma patients are presented in Table 2. Treatment significantly reduced FPG, HbA1c, and LDL cholesterol levels (P<0.05 for all). Although there was an improvement in other lipid parameters, fasting insulin, BMI, and HOMA-IR compared to the baseline, the differences were not statistically significant.

Initially, 12 patients had impaired fasting glucose. After treatment, FPG returned to normal in six patients (50%). Data on glucose metabolism of these 12 patients are shown in Table 3. FPG, HbA1c, insulin, and HOMA-IR changes in patients with impaired glucose metabolism were statistically significant (P<0.05 for all). Although there was a decrease in all glucose parameters compared to the baseline after treatment in 90 patients with normal glucose metabolism at the beginning, only the reduction in HbA1c was significant (P<0.01, Table 4). Hypoglycemia, defined as FPG < 65 mg/dL [9], was not observed in any patient.

There were 25 patients with LDL cholesterol levels >130 mg/dL at diagnosis. In 10 (40%), LDL cholesterol level decreased to normal after cabergoline treatment. This group's LDL cholesterol change was significant (baseline: 165.6 mg/dL, last visit: 140.6 mg/dL, P=0.002). There were 20 patients with triglyceride levels above 150 mg/dL at diagnosis. After cabergoline treatment, the triglyceride level of seven patients (35%) returned to normal. The triglyceride change in this group was insignificant (baseline: 273.9 mg/dL, last visit: 215.1 mg/dL, P=0.141). There were 12 patients with HDL cholesterol levels <50 mg/dL in women and <40 mg/dL in men at diagnosis. After cabergoline treatment, HDL cholesterol increased to normal in six patients (50%). However, this increase was not statistically significant (baseline: 36.9 mg/dL, last visit: 40.9 mg/dL, P=0.082).

Factors Affecting the Changing Metabolic Parameters

A correlation analysis was performed to identify fac-

Table 1. General characteristics of patients with prolactinoma

Characteristics	Patients with prolactinoma (n=102)
Sex (female), n (%)	64 (62.7%)
Age at diagnosis (years)	32.7±12.5
Largest adenoma diameter at diagnosis (mm)	10 (8-21)
Prolactin at diagnosis (ng/mL)	226 (109-691)
Maximum cabergoline dose (mg/week)	1 (0.5-2)
Cumulative cabergoline dose (mg)	60 (20-150)
Cabergoline usage time (months)	20 (10-50)
Disease duration (months)	36 (18-60)
Largest adenoma diameter at last visit (mm)	5 (3-12)
Prolactin at last visit (ng/mL)	12 (5-30)
Presentation, n (%)	
Galactorrhea	39 (38.2)
Oligomenorrhea	45 (44.1)
Erectile dysfunction	17 (16.7)
Loss of libido	21 (20.6)
Infertility	5 (4.9)
Visual field deficit	15 (14.7)

Data are shown as mean±standard deviation or median (interquartile range) or n (%)

tors influencing the fasting plasma glucose, HbA1c, and LDL cholesterol levels measured at the final visit in prolactinoma patients. The results are presented in Table 5. The analysis showed that only the cumulative dose of cabergoline used significantly affected all three metabolic parameters (P<0.05 for all).

DISCUSSION

In this study, the metabolic changes in a group of prolactinoma patients treated with cabergoline were longitudinally evaluated. After a median follow-up of three years, the patients' fasting plasma glucose,

Table 2. Comparison of metabolic parameters evaluated at diagnosis and last visit in patients with prolactinoma°

Parameters	At diagnosis	At last visit	OR	95% CI	P value
Plasma glucose (mg/dL)	88.7±19.1	83.9±11.8	2.004	1.987–3.654	**0.048**
Insulin (µU/mL)	14.1±9.4	12.2±6.7	1.584	-0.502–4.273	0.119
HbA1c (%)	5.5±0.5	5.2±0.7	4.019	0.172–0.509	**0.001**
HOMA-IR	2.9±1.2	2.6±1.6	1.487	-0.121–0.803	0.144
Total cholesterol (mg/dL)	193.5±41.7	187.9±39.7	1.429	-2.223–13.357	0.158
LDL-cholesterol (mg/dL)	125.4±37.7	113.5±35.4	3.352	4.839–19.095	**0.001**
HDL-cholesterol (mg/dL)	54.9±14.6	55.3±14.5	-0.273	-2.636–2.001	0.786
Triglyceride (mg/dL)	136.9±58.9	128.5±96.4	0.654	-17.421–34.381	0.515
BMI (kg/m^2)	27.1±3.2	26.9±3.4	0.785	-1.527–1.912	0.711

Data are shown as mean±standard deviation. BMI=body mass index, CI=confidence interval, HDL=high-density lipoprotein, HOMA-IR=Homeostatic model assessment-insulin resistance, LDL=low-density lipoprotein, OR=odds ratio

Table 3. Changes in glucose metabolism with treatment in patients with impaired glucose metabolism at baseline

Parameters (n=12)	At diagnosis	At last visit	OR	95% CI	P value
Plasma glucose (mg/dL)	117.6±29.2	104.8±18.5	3.114	0.487–0.554	**0.003**
Insulin (µU/mL)	19.9±9.8	16.1±8.7	5.584	0.102–0.273	**0.001**
HbA1c (%)	6.1±0.5	5.8±0.7	1.011	-0.163–0.487	0.140
HOMA-IR	4.6±1.8	3.5±1.7	1.487	0.213–0.312	**0.001**

Data are shown as mean±standard deviation. CI=confidence interval, HOMA-IR=Homeostatic model assessment-insulin resistance, OR=odds ratio

HbA1c, and LDL cholesterol levels significantly decreased compared to baseline. In patients with initially impaired glucose metabolism, glucose metabolism returned to normal in 50% of patients with treatment. In addition, 40% of patients with high LDL cholesterol levels achieved normal LDL levels with cabergoline treatment. Moreover, a significant relationship was found between these parameters and the cumulative dose of cabergoline used. It was observed that as the cumulative cabergoline dose increased, the reductions in these metabolic parameters were more pronounced. It is well-established that elevated prolactin levels in prolactinoma patients are associated with metabolic disorders [3]. Previous studies have reported hyperglycemia, hyperlipidemia, and increased BMI in patients with prolactinoma [10-37]. Dopamine agonists, particularly cabergoline, one of the primary treatments for prolactinoma, have been shown to have beneficial effects on these metabolic disturbances. In patients who achieve normoprolactinemia with treatment, improvements in metabolic abnormalities are observed [24-28]. These improvements are attributed to normalization of prolactin levels and the positive metabolic effects of cabergoline [31-33]. The beneficial effects of dopamine agonists on metabolic disorders have been demonstrated even in patients without hyperprolactinemia [24].

Prolactin receptors have been identified in insulin-secreting pancreatic beta cells [16]. Elevated prolactin levels lead to an increase in both beta cell mass and insulin secretion [17]. Additionally, dopamine receptors (D2DR) are also present in beta cells, and the administration of dopamine agonists, such as cabergoline, reduces insulin secretion from the pancreas [38]. Glucose profile and insulin resistance improvements have been reported in prolactinoma patients following cabergoline treatment [26, 27]. Long-term cabergoline therapy has been shown to reduce fasting insulin and HOMA-IR levels, correlating with the cumulative dose of cabergoline [33]. In our study, fasting plasma glucose and HbA1c levels significantly decreased with treatment. However, although insulin and HOMA-IR levels decreased compared to baseline, the changes did not reach statistical significance. The improvement in glucose profiles observed in our study was strongly correlated

Table 4. Changes in glucose metabolism with treatment in patients with normal glucose metabolism at baseline

Parameters (n=90)	At diagnosis	At last visit	OR	95% CI	P value
Plasma glucose (mg/dL)	85.5±18.1	84.6±16.3	2.025	-0.564–0.162	0.052
Insulin (µU/mL)	13.4±6.4	10.6±7.6	4.357	-0.814–0.581	0.140
HbA1c (%)	5.4±0.6	5.2±0.5	1.011	0.175–0.339	**0.001**
HOMA-IR	2.4±1.0	2.3±1.1	3.245	-0.314–0.124	0.120

Data are shown as mean±standard deviation. CI=confidence interval, HOMA-IR=Homeostatic model assessment-insulin resistance, OR=odds ratio

Table 5. Evaluation of factors affecting metabolic parameters that showed significant changes during follow-up using correlation analysis

Metabolic parameters	Cumulative cabergoline dose		Disease duration		Prolactin at last visit	
	P value	r-value*	P value	r-value*	P value	r-value*
Fasting plasma glucose	**0.038**	-0.211	0.097	-0.047	0.226	-0.017
HbA1c	**0.012**	-0.316	0.091	-0.036	0.317	-0.046
LDL-cholesterol	**0.006**	-0.418	0.076	-0.012	0.199	-0.032

*The r value expresses the direction and coefficient of correlation.
LDL: low-density lipoprotein

with the cumulative cabergoline dose. Our findings support the hypothesis that, in addition to prolactin normalization, cabergoline has a beneficial effect on glucose metabolism regulation.

Dyslipidemia has been frequently reported in prolactinoma patients and is characterized by increased total cholesterol, LDL, triglycerides, and decreased HDL levels [35, 36, 39]. Hyperprolactinemia is thought to be responsible for this unfavorable lipid profile by inhibiting apolipoprotein biosynthesis [37]. In our study, improvements in lipid metabolism were observed after treatment compared to baseline. Notably, there was a significant reduction in LDL levels following treatment. Although positive changes were also noted in other lipid parameters, these did not reach statistical significance. Additionally, the improvement in the lipid profile was correlated with the cumulative dose of cabergoline used.

Hyperprolactinemia can lead to increased appetite, weight gain, and obesity [10-14]. Prolactinoma patients have been reported to have higher body fat mass than healthy controls [39]. Moreover, elevated prolactin levels may result from metabolic risk factors such as waist circumference and visceral fat accumulation. It is believed that long-term treatment with cabergoline may improve waist circumference and body composition. Notably, in hypogonadal male prolactinoma patients, the addition of testosterone replacement therapy to cabergoline treatment has been associated with more pronounced improvements in body composition [40]. In our study, although a decrease in BMI was observed after treatment in prolactinoma patients, it did not reach statistical significance. This may be due to excluding hypogonadal patients receiving replacement therapy, in whom improvements are likely more pronounced. Additionally, our study did not perform waist circumference and visceral fat measurements, which may explain the lack of significant changes observed.

This study confirmed that metabolic improvements were observed in prolactinoma patients when disease control was achieved through treatment. Our results suggest that these improvements may be attributed not only to the achievement of normoprolactinemia but also to the beneficial metabolic effects of cabergoline. However, our study has some limitations. First, the causal relationship at the molecular level between metabolic parameters, prolactin, and cabergoline was not established. Nevertheless, the metabolic improvements observed in a relatively large cohort with long-term follow-up are likely attributable to prolactin normalization and cabergoline treatment. Additionally, only patients without gonadal dysfunction were included in the study, meaning that the results are independent of gonadal replacement therapy. Since all patients achieved normoprolactinemia, the findings likely reflect the positive metabolic effects of cabergoline. Another limitation is that patients treated with other modalities, such as surgery, were excluded. However, surgery in our center is typically reserved for more challenging prolactinoma cases [41, 42], which often present with additional hormonal disturbances that could affect the outcomes [43]. A further limitation is the lack of advanced metabolic assessments. Due to the study's retrospective nature, more detailed evaluations, such as oral glucose tolerance tests, apolipoprotein measurements, waist circumference, and body composition analyses, were unavailable. Future prospective, large-scale, and molecular-level studies could provide stronger evi-

dence and highlight metabolic restoration as a therapeutic goal in prolactinoma patients.

CONCLUSION

Prolactin is a hormone with widespread metabolic effects, and elevated prolactin levels have been clearly shown to negatively impact metabolism in prolactinoma patients. Achieving normoprolactinemia through appropriate treatment is critical in restoring these patients' metabolic balance. However, cabergoline provides direct metabolic benefits beyond normalizing prolactin levels. Current and future research suggests that dopamine agonists like cabergoline may represent a powerful therapeutic option not only for prolactinoma patients but also for individuals suffering from metabolic disorders who do not have hyperprolactinemia. This opens up a new and promising treatment avenue for managing metabolic disorders in broader patient populations with dopamine agonists.

Ethics Committee Approval
The study adhered to the ethical principles for medical research involving human participants described in the World Medical Association's Declaration of Helsinki. The Ethics Committee of Istanbul University-Cerrahpasa approved the study (Approval Number: 16.10.2023-711105).

Authors' Contribution
Study Conception: AND, AB, DÖ, SŞ, PK; Study Design: AND, AB, DÖ, SŞ, PK; Supervision: AND, AB, DÖ, SŞ, PK; Funding: N/A; Materials: AND, AB, DÖ, SŞ, PK; Data Collection and/or Processing: AND, AB, DÖ, SŞ, PK; Statistical Analysis and/or Data Interpretation: AND, AB, DÖ, SŞ, PK; Literature Review: AND, AB, DÖ, SŞ, PK; Manuscript Preparation: AND, AB, DÖ, SŞ, PK and Critical Review: AND, AB, DÖ, SŞ, PK.

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Diagnostic performance of ultrasound versus 99mTc-sestamibi scintigraphy in preoperative depiction and localization of parathyroid adenoma in patients with primary hyperparathyroidism

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ABSTRACT

Objectives: To evaluate diagnostic performance of ultrasound (US) and 99mTc-sestamibi scintigraphy (MIBI) in preoperative depiction and localization of parathyroid adenoma in patients with primary hyperparathyroidism (PHPT)

Methods: A total of 645 patients (mean age: 52.3 [range; 18-81] years, 72.9% were females) who underwent parathyroidectomy for PHPT due to histopathologically-confirmed adenoma were included in this retrospective cohort study. The accuracy of preoperative US and MIBI in the depiction and localization of parathyroid adenomas was evaluated with respect to intraoperative localization.

Results: Preoperative MIBI was more accurate than preoperative US in identifying upper right (6.2% vs. 2.6%) and upper left (7.5% vs. 3.8%) orthotopic adenomas, and ectopic adenomas (1.5% vs. 0.7%). Failure to identify an adenoma was less commonly noted on preoperative MIBI than on preoperative US (26.9% vs. 32.8%). The US mainly failed to diagnose the adenomas located in the upper left (27.4%), lower left (25.9%) and upper right (19.3%) orthotopic sites, while MIBI mainly missed those located in the lower left (36.2%), lower right (24.7%) and upper left (20.1%) orthotopic sites. True-positive depiction rates on the preoperative US (60.4% for ≤250 mg, 80.3% for ≥901 mg) and MIBI (56.7% for ≤250 mg, 86.7% for ≥901 mg) were increased as the parathyroid weight increased.

Conclusions: Our findings indicate inconclusive results in the identification of parathyroid adenoma in nearly one-third of cases with both US and MIBI and the side-specific and site-specific variations in their performance. Hence, the combined use of these imaging modalities may be of great clinical value in the precise preoperative depiction and localization of parathyroid adenomas.

Keywords: Primary hyperparathyroidism, preoperative imaging, ultrasound, 99mTc-sestamibi scintigraphy, parathyroid adenoma, localization

Primary hyperparathyroidism (PHPT), a common endocrine disorder associated with an overactive parathyroid gland, is caused by a parathyroid adenoma in majority of cases, followed by hyperplasia and rarely carcinoma of the parathyroid gland [1].

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Surgical resection of pathological parathyroid glands via bilateral neck exploration (BNE) or minimally invasive focused parathyroidectomy (MIP) is the only definite treatment for PHPT [2]. Owing to an improved presurgical imaging technology enabling the implementation of a less extensive but similarly effective surgical approach, a dramatic shift has occurred in the surgical practice over the last two decades, with increasing use of MIP over traditional BNE in PHPT patients [2, 3]. Hence, MIP has become the surgery of choice in solitary adenomas, which provides high surgical cure rates along with lower complication rates, shorter surgery duration, and hospital stay, and improved cosmetic results when compared to BNE [4, 5].

Accordingly, preoperative imaging has become increasingly important in clinical practice as the success of MIP is highly dependent on the accurate preoperative detection and localization of abnormal parathyroid lesions [6,7]. Preoperative imaging enables not only the lateralization and the exact location of abnormal glands but also helps the surgeon with the qualification of patients who would be better served with BNE or MIP [4, 5].

The ultrasound (US) and 99mTc-sestamibi scintigraphy (MIBI) are considered the first-line imaging modalities for the preoperative detection and localization of parathyroid adenomas [4, 6-9]. However, the reported sensitivities of neck US and MIBI scans range from 65% to 81.4% and from 61.0% to 90.6%, respectively, and up to 20% of preoperative imaging results are considered inconclusive [4, 8, 10, 11].

Nonetheless, most of the studies addressing the diagnostic performance of preoperative imaging modalities are small scale studies without detailed analysis of adenoma localization (i.e., lateralization or site-specific characteristics) and the optimal preoperative localization technique remains to be inconclusive [6, 8, 10-12].

This retrospective single-center study aimed to comparatively evaluate the performance of preoperative imaging modalities (US and MIBI) in preoperative depiction and localization of parathyroid adenoma in a homogenous surgical cohort of patients with PHPT, using a detailed 4-quadrant side/site-specific analysis.

METHODS

Study population

A total of 645 patients (mean age: 52.3 [range; 18-81] years, 72.9% were females) who underwent parathyroidectomy for PHPT due to histopathologically-confirmed adenoma were included in this single-center retrospective cohort study conducted at a tertiary care general surgery clinic between January 2005 and June

Table 1. Patient demographics, preoperative laboratory findings and surgical approach

Patient demographics	
Age (year), mean (min-max)	52.3 (18-81)
Gender, n (%)	
Female	470(72.9)
Male	175(27.1)
Preoperative laboratory findings, median (min-max)	
Serum calcium (mEq/L)	9.1(8.3-13.2)
Serum PTH (pg/mL)	148(111-1867)
Surgical approach, n (%)	
Minimally invasive focused parathyroidectomy (MIP)	356(55.2)
Bilateral neck exploration (BNE)	289(44.8)
Initial choice	*239(37.1)*
Converted from MIP	*50(7.7)*

PTH=parathyroid hormone

2023. The presence of preoperative US and MIBI reports, and the confirmed postoperative histopathological diagnosis of parathyroid adenoma or hyperplasia were the study's inclusion criteria. Patients without preoperative imaging data (US or MIBI), those without a confirmed histopathological diagnosis of adenoma or hyperplasia, and those with postoperative recurrence or persistence were excluded from the study.

Written informed consent was obtained from each participant. This study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the Bursa Uludag University Clinical Research Ethics Committee (Date of Approval: 19/09/2023; Protocol No: 2023-17/60).

Assessments

Patient demographics (age, gender), preoperative parathyroid hormone (PTH) and calcium levels, and preoperative imaging data on 4-quadrant adenoma localization were recorded in each patient. The accuracy of preoperative US and MIBI in depiction and localization of parathyroid adenomas was evaluated with respect to intraoperative localization which was defined as a reference of the localization diagnostics. The intraoperative parathyroid adenoma localization and the true-positive US and MIBI depiction rates were also evaluated with respect to parathyroid weight.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, version 22.0. Armonk, NY: IBM Corp). Descriptive statistics were reported including means and ranges for continuous variables and percentages for categorical variables. Data were expressed as mean, median (minimum-maximum), and percent (%) where appropriate.

RESULTS

Patient Demographics, Preoperative Laboratory Findings, and Surgery Type

The mean patient age was 52.3 (range: 18-81) years, and females composed the 72.9% of the study population. Median levels for preoperative serum calcium and serum PTH were 9.1 (8.3-13.2) mEq/L and 148 (111-1867) pg/mL, respectively (Table 1).

All patients with solitary adenoma detected on preoperative imaging were operated with MIP (n=356, 55.2%), while those with multi-gland disease or suspicious/negative imaging were operated with BNE (n=289, 44.8%). The operation was initially started with MIP but then converted to BNE in 50 of 289 BNE-operated patients (Table 1).

Preoperative Imaging with Respect to Intraoperative Localization

Intraoperative localization revealed that most of parathyroid adenomas were located inferiorly (73.2%)

Table 2. Parathyroid adenoma localization: Preoperative US and MIBI with respect to intraoperative assessment

	Preoperative US (n=645)	Preoperative MIBI (n=645)	Intraoperative findings (n=645)
Adenoma localization, n (%)			
Orthotopic			
Lower left	206 (31.9)	198 (30.8)	261 (40.4)
Lower right	176 (27.2)	169 (25.9)	212 (32.8)
Upper left	25 (3.8)	48 (7.2)	83 (12.8)
Upper right	17 (2.6)	40 (6.2)	58 (8.9)
Ectopic	5 (0.7)	10 (1.5)	19 (2.9)
Bilateral	4 (0.6)	6 (0.9)	12 (1.8)
Not found	212 (32.8)	174 (26.9)	

US=Ultrasound, MIBI=99mTc-sestamibi scintigraphy

Table 3. Distribution of missed parathyroid adenoma diagnoses by preoperative US (n=212) and MIBI (n=174)

		Missed diagnoses by preoperative imaging		Intraoperative reference data on localization diagnostics
		Preoperative US	Preoperative MIBI	
Orthotopic, n (%)				
Inferior	Lower left	55 (25.9)	63 (36.2)	261
	Lower right	36 (17.0)	43 (24.7)	212
Superior	Upper left	58(27.4)	35 (20.1)	83
	Upper right	41 (19.3)	18 (10.3)	58
Ectopic, n (%)		14 (6.6)	9 (5.2)	19
Bilateral, n (%)		8 (3.8)	6 (3.5)	12
Total		212 (100.0)	174 (100.0)	

US: Ultrasound; MIBI: 99mTc-sestamibi scintigraphy Shaded areas indicate better performance of the imaging modality

including the lower left (40.4%) or lower right (32.8%) orthotopic sites. Preoperative US and MIBI, although at a lower rate than the intraoperative assessment, identified the lower right (27.2% and. 25.9%) and the lower left (31.9% vs. 30.8%) orthotopic adenomas with similar accuracy (Table 2).

Intraoperatively, only 21.7% of parathyroid adenomas were located superiorly including the upper left (12.8%) or upper right (8.9%) orthotopic sites, while ectopic (2.9%) and bilateral (1.8%) adenomas were the least commonly identified ones (Table 2).

The preoperative MIBI, compared with the preoperative US, was more accurate in identifying adenomas in the less-common localizations such as the

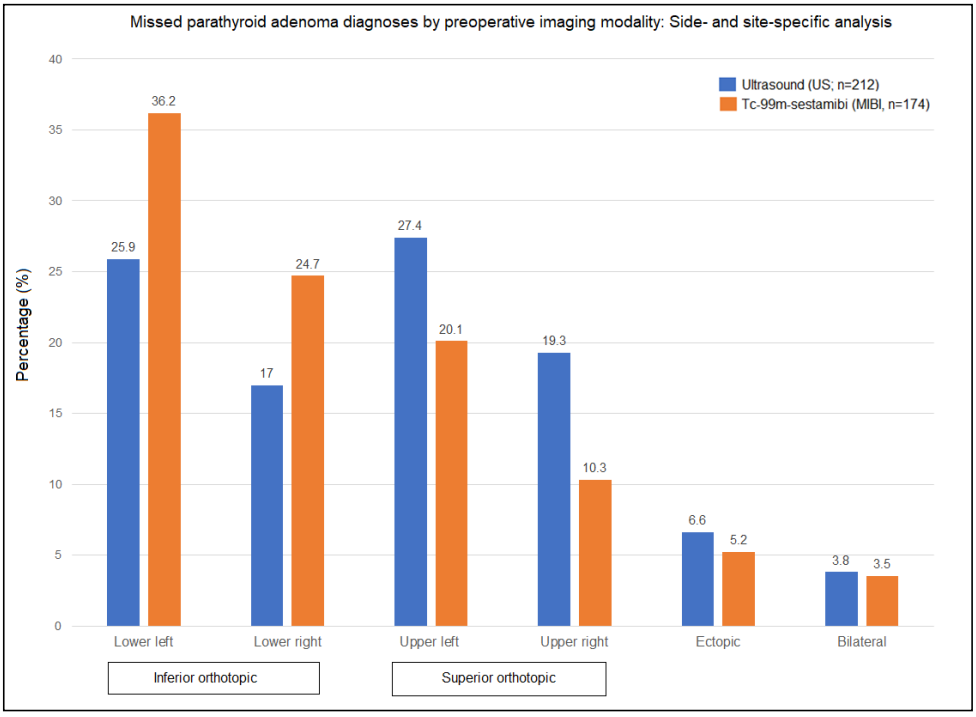

Fig. 1. Side- and site-specific analysis of the missed parathyroid adenoma diagnosis by preoperative US (n=212) and MIBI (n=174).

Table 4. Intraoperative localization and true-positive US and MIBI depiction rates according to parathyroid weight

	Parathyroid weight (mg)			
	≤250 mg	**251-500 mg**	**501-900 mg**	**≥901 mg**
Intraoperative parathyroid adenoma localization, n (%)				
Unilateral adenoma (n=614)	**162 (26.4)**	**165 (26.9)**	**151 (24.6)**	**136 (22.1)**
Bilateral adenoma (n=12, total 24)	7 (29.2)	9 (37.5)	5 (20.8)	3 (12.5)
Ectopic adenoma (n=19)	6 (31.6)	7 (36.8)	4 (21.1)	2 (10.5)
True positive depiction on preoperative imaging, n(%)				
True positive US (n=424)	98/162 (60.4%)	104/165 (75.4%)	110/151 (80.1%)	112/136 (80.3%)
True positive MIBI (n=455)	92/162 (56.7%)	118/165 (71.5%)	127/151 (84.1%)	118/136 (86.7%)

US=Ultrasound, MIBI=99mTc-sestamibi scintigraphy

upper right (6.2% vs. 2.6%) and the upper left (7.5% vs. 3.8%) orthotopic adenomas, as well as the ectopic (1.5% vs. 0.7%) adenomas. Failure to locate an adenoma was less commonly noted on preoperative MIBI than on preoperative US (174 missed locations [26.9%] vs. 212 missed locations [32.8%], respectively) (Table 2).

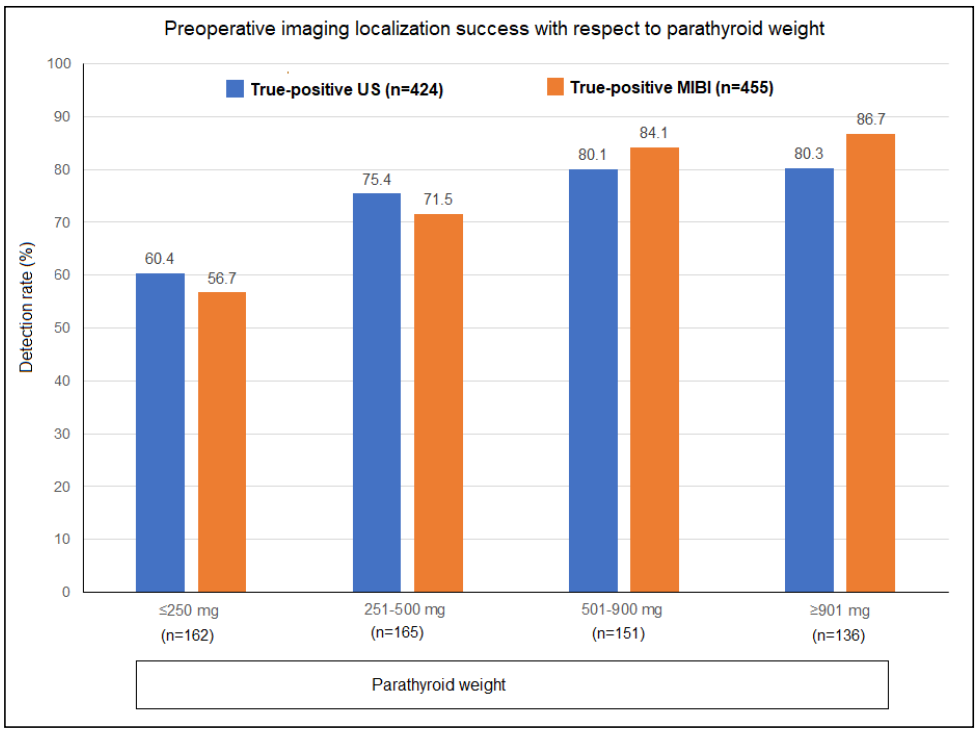

Fig. 2. Preoperative imaging success in localization of adenoma with respect to parathyroid weight.

Distribution of Missed Locations by Preoperative US (n=212) and MIBI (n=174)

Overall, preoperative US mainly missed the adenomas located in the upper left (27.4%), lower left (25.9%) and upper right (19.3%) orthotopic sites. Lower left (36.2%), lower right (24.7%) and upper left (20.1%) orthotopic sites comprised the majority of missed adenoma localizations on preoperative MIBI (Table 3, Fig. 1).

The left-sided adenomas were more disadvantageous than the right-sided adenomas in terms of being recognized on preoperative imaging, regardless of the imaging modality; whereas US more accurately identified the inferiorly located adenomas and MIBI more accurately identified the superiorly located adenomas (Fig. 1).

Intraoperative Localization and True-positive US and MIBI Depiction Rates According to Oarathyroid Weight

Intraoperative findings revealed that parathyroid weight groups were equally presented in unilateral adenoma cases, while parathyroid weight <500 mg was more common than greater parathyroid weights in bilateral and ectopic adenomas (Table 4).

True-positive depiction rates on preoperative US (from 60.4% for ≤250 mg to 80.3% for ≥901 mg) and MIBI (from 56.7% for ≤250 mg to 86.7% for ≥901 mg) were increased as the parathyroid weight increased (Table 4, Fig. 2).

DISCUSSION

In this single-center retrospective study in a homogenous surgical cohort of PHPT patients treated over 18 years, preoperative imaging failed to identify nearly one-third of parathyroid adenomas detected intraoperatively (32.8% by US and 26.9% by MIBI). Regarding intraoperative findings, the US and MIBI modalities showed similar accuracy in correctly identifying the adenomas located in more prevalent anatomic sites (i.e., inferior orthotopic sites). However, their performance differed in less-prevalent anatomic sites (i.e., superior orthotopic sites, ectopic location) in favor of MIBI. Specifically, both the US and MIBI failed to localize primarily the left-sided adenomas, along with a site-specific variation in the risk of a missed diagnosis. This risk of a missed diagnosis was lower with US for the adenomas located in the inferior orthotopic sites and was lower with MIBI for those located in the superior orthotopic sites.

Our intraoperative assessment revealed that most parathyroid adenomas were located inferiorly (73.2%) at the lower left (40.4%) or lower right (32.8%) orthotopic sites, while 21.7% were located superiorly at the upper left (12.8%) and the upper right (8.9%) orthotopic sites and only 2.9% were ectopic adenomas. These findings support the consistently reported preponderance of lower orthotopic sites as the most common parathyroid adenoma location in large series of PHPT patients, including those from Turkey which indicated the lower left location in more than 40% of adenomas [10, 13, 14].

In our cohort, preoperative MIBI was associated with certain advantages over the US such as the lower rate of missed diagnoses overall (26.9% vs. 32.8%, respectively), and more common diagnoses of superiorly located adenomas and ectopic adenomas. Similarly, previous studies from Turkey also indicated the association of MIBI vs. US with a more common detection of single parathyroid adenoma, as well as with a higher sensitivity (70 vs. 60% and 92.17 vs. 75.89%), accuracy (90.9 vs. 87.1% and 87.60 vs. 70.25%) and positive predictive value (PPV; 94.64% vs. 90.43%) in identifying parathyroid adenomas [15, 16]. Also, in a meta-analysis of 12 studies on the performance of preoperative imaging in identifying parathyroid adenomas, the pooled sensitivity of the US and MIBI was found to be similar (83% vs. 80%), while the pooled estimate of MIBI specificity was significantly higher than the US [17].

Indeed, technical advances, such as hybrid Single Photon Emission Computed Tomography/ Computed Tomography (SPECT/CT) acquisition is considered likely to account for the higher sensitivity, specificity, and accuracy of MIBI compared to US, enabling a more precise preoperative depiction of parathyroid adenomas, mainly those in ectopic locations (i.e., retro tracheal, retrosternal, upper mediastinal and intrathymic regions) [4, 6, 9, 11].

Accordingly, in a recent study with 213 PHPT patients, preoperative MIBI SPECT/CT was found to show higher sensitivity (84% vs. 72%) and accuracy (80% vs. 71%) compared to the US, and to enable greater anatomical precision (75.8% vs 68.7%) even

in the case of ectopic glands or coexisting thyroid pathology [11].

Moreover, in a recent study by Van den Bruel *et al*. [7] in 104 PHPT patients, the correct identification and misclassification rates by US and MIBI for the upper (70.7% and 48.3% on US; 54.1% and 55.0% on MIBI) and lower (78.7% and 10.4% on US; 59.3% and 2.9% on MIBI) adenomas showed that nearly one-third of superior adenomas detected intraoperatively were called inferior by preoperative imaging. Indeed, in accordance with the embryological development of the parathyroid glands from the branchial pouches, the lower and upper parathyroids are more correctly called P3 and P4, respectively by virtue of cross-migration from the respective pockets, while the superior parathyroid glands growing downwards posteriorly can be mistaken for the lower ones. This upper/lower mispositioning by imaging is suggested to be related to the inability to visualize anatomical landmarks (i.e., the recurrent laryngeal nerve, inferior thyroid artery) as a reference point, by any imaging modality [7, 18]. Considering the risk of misdiagnosis attributable to each preoperative imaging modality, our findings indicate the left-sided orthotopic glands to be less often diagnosed by both US and MIBI, along with higher performance of US for inferiorly located adenomas and that of MIBI for superiorly located and ectopic adenomas. Nonetheless, there is no current universally accepted algorithm for imaging localization in the setting of PHPT, while the studies also revealed controversial data on the overall, and site- or side-specific diagnostic performance of preoperative imaging modalities in PHPT patients.

In a retrospective series of 1089 operated PHPT patients by Iwen *et al*., MIBI and US were associated with failure to identify the gland in 29.8% and 29.4% of patients, respectively, while ectopic and orthotopic upper glands were much less often diagnosed by both MIBI and US [10]. Iwen *et al*. [10] also reported that the sensitivity of US and MIBI was higher for lower left (68.9% and 72%, respectively) adenomas, while their specificity was higher for upper right (99.2% and 99.1%, respectively) adenomas.

Adkisson *et al*. [12] reported the association of both US and MIBI with similarly high rates of accurate preoperative identification of inferiorly located adenomas, whereas a higher rate of accurate adenoma localization by US compared to MIBI (63% vs. 41%). De Simone *et al*. [19] reported the correct detection and failure rates for superior adenomas (56.25% and 43.75% for US and 37.5% and 62.5% for MIBI) and inferior adenomas (86.66% and 13.33% for US and 68.88% and 13.33% for MIBI), indicating higher sensitivity of US for inferior solitary adenoma and lower sensitivity of MIBI for superior adenoma. Other studies also reported higher accuracy (93% vs. 90% and 93 vs. 63%) and sensitivity (98% vs. 93%, 88.0% vs. 63.0% and 91.5 vs. 56.1%) of US vs. MIBI in the preoperative localization of parathyroid adenomas [6, 20].

Nonetheless, for such retrospective series studies over long time periods, the imaging findings are subject to interobserver differences or change in hospital protocols over time [10]. Importantly, there are certain factors affecting the diagnostic accuracy of preoperative imaging for localizing abnormal glands, such as differences in patient population (better performance in SGD than in MGD), differences in imaging acquisition (lower diagnostic accuracy for use of planar scintigraphy imaging alone vs. in combination with SPECT), the method of analysis used for imaging results and surgical reference standards (per-patient or per-lesion/quadrant), concomitant thyroid pathology (decreases US sensitivity), gland weight, the size of adenoma (higher MIBI sensitivity for larger adenomas) and cellular composition of abnormal parathyroid nodules (higher MIBI sensitivity for oxyphil cells) [2, 4-6, 11, 21].

Notably, the association of greater parathyroid weight with increased likelihood of true-positive depiction rates on US (>80% detection rate for weight >501 mg) and MIBI (>86% detection rate for weight >901 mg) in our study supports the impact of the parathyroid weight on the success rate of localization studies with decrease in the localization sensitivity for the minimally enlarged parathyroid adenomas on preoperative imaging [11, 21-24]. Accordingly, previous studies indicated significantly lower parathyroid weights in patients preoperatively mis-localized on US [22], improved MIBI-PS sensitivity when the gland weight is greater than 600 mg [21] as well as significantly higher parathyroid weight in MIBI-positive cases than in MIBI-negative cases (1145.9 mg vs. 692.2 mg) [11].

MIP is the preferred surgical approach in patients with single-gland disease (solitary adenoma) detected on preoperative imaging, while BNE is performed in

patients with multi-gland disease (>2 abnormal glands) or with negative imaging [2, 4, 5]. In the current study, the operation was initially started as MIP but then converted to BNE in 50 (7.7%) patients, emphasizing the role of a focused surgical approach even when preoperative imaging modalities indicate a single adenoma, and surgeons should always be prepared to convert from a MIP into BNE if intraoperative findings show multiglandular disease [4, 6, 8, 10, 14].

In fact, given the likelihood of inconclusive results in nearly one-third of PHPT patients by use of US or MIBI alone, and site-specific advantages pertaining to each modality, the combination of both methods may be of great clinical value to obtain the best diagnostic results for precise preoperative visualization of parathyroid adenoma [4, 6, 8, 9, 25]. US-scan is an operator- and instrument-dependent procedure limited to the anterior region of the neck which is also hampered by the concomitant thyroid pathology [4, 9, 25]. However, MIBI-scan, recently integrated with CT-SPECT technique, ranges up to the mediastinum, and is considered an operator-independent procedure less hampered by thyroid enlargement and ideal for ectopic sites [6, 8, 9]. In this regard, the integration of US and MIBI procedures offers greater opportunity for side/site location [4, 6, 8, 9, 25]. Many studies indicated the favorable performance of the combined use of US and MIBI-SPECT/CT in terms of accuracy of preoperative imaging in the setting of PHPT, based on the superiority of MIBI to US in detection of ectopic adenomas, the consideration of US to be useful in cases with low intensity retention of MIBI and the widespread availability and cost-effectiveness of this strategy [4, 6, 8, 9, 26-30].

Limitations

This study has some limitations. First, due to retrospective single-center design, establishing the temporality between cause and effect as well as generalizing our findings to overall PHPT population seems difficult. Second, while the findings were achieved in a homogenous surgical cohort of PHPT patients treated over an 18-year period, inter-operator variability in radiological imaging is another potential limitation with likely effects on results. Third, inability to assess the potential impact of imaging studies on the surgical approach, due to retrospective design, as well as the likelihood of overestimated preoperative imaging performance due to inclusion of only surgical patients are other limitations.

CONCLUSION

In conclusion, this retrospective analysis in a homogenous surgical cohort of PHPT patients revealed the association of preoperative imaging modalities with inconclusive results regarding the identification of parathyroid adenoma in nearly one-third of cases. Left-sided orthotopic glands were less often diagnosed by both US and MIBI, along with higher performance of US for inferiorly located adenomas and that of MIBI for superiorly located adenomas as well as ectopic adenomas. Given the side-specific and site-specific variations in the performance of each imaging modality, our findings emphasize the likelihood of combined use of both modalities to be of great clinical value in the precise preoperative depiction and localization of parathyroid adenomas in patients with PHPT.

Ethics Committee Approval

Written informed consent was obtained from each participant. This study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the Bursa Uludag University Clinical Research Ethics Committee (Date of Approval: 19/09/2023; Protocol No: 2023-17/60).

Authors' Contribution

Study Conception: EG; Study Design: EG; Supervision: EG; Funding: N/A; Materials: EG; Data Collection and/or Processing: EG; Statistical Analysis and/or Data Interpretation: EG; Literature Review: EG; Manuscript Preparation: EG and Critical Review: EG.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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Corneal topographic and aberrometric changes in patients with acquired blepharoptosis after levator resection surgery

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ABSTRACT

Objectives: To evaluate changes in corneal topography and aberrometry in patients with acquired blepharoptosis after levator resection surgery.

Methods: This prospective, interventional study evaluated 30 eyelids of 19 patients who underwent levator resection surgery for acquired blepharoptosis with fair and good levator function (LF). Patients underwent corneal topography before and 3 months after surgery.

Results: Eleven patients had bilateral, and 8 patients had unilateral surgery. There were significant decreases in steep keratometry (K2) (preoperative: 46.21±5.02, postoperative: 44.58±2.11, P=0.046) and corneal astigmatism (preoperative: 2.98±0.61, postoperative: 1.59±1.50, P=0.034). There were no statistically significant differences between the preoperative and postoperative values of flat keratometry (K1) (P=0.585), mean keratometry (Kmean) (P=0.122), axis of corneal astigmatism (P=0.548), central corneal thickness (P=0.350), anterior chamber depth (P=0.747) and anterior chamber volume (P=0.679). The root mean square (RMS)-higher order aberrations (HOA) (P<0.001), RMS-Coma (Z_3^1) (P<0.001), and RMS-Trefoil (Z_3^3) (P=0.005) decreased significantly. Preoperative and postoperative values of the seconder astigmatism (P=0.345), RMS-spherical aberration (Z_4^0) (P=0.255), and RMS-Quadrafoil (Z_4^4) values were found similar.

Conclusions: Levator resection for acquired blepharoptosis can improve the topography and aberrometry measurements of the cornea 3 months after surgery.

Keywords: Blepharoptosis, levator resection surgery, corneal topography, corneal higher-order aberrations, RMS-HOA, dry eye

Blepharoptosis, also known as "ptosis," is the unilateral or bilateral drooping of the upper eyelid in the primary gaze position of the eye. It is classified as congenital or acquired. Congenital ptosis is a myogenic origin in which the levator muscle improperly develops and occurs at birth or in the first year of life. Acquired ptosis appears later and can be sub-classified: neurogenic, myogenic, aponeurotic, mechanical, and traumatic. The most common is aponeurotic ptosis, which develops due to involutional changes, dehiscence, or disinsertion of aponeurosis [1, 2]. The estimated prevalence of ptosis in the adult population varies between 4.7% and 13.5% [3-5].

Blepharoptosis may cause both appearance-related

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anxiety and poor visual quality [6, 7]. In patients with blepharoptosis, visual field loss, refraction changes, and decreased contrast sensitivity have been shown [8-10].

Depending on the severity of blepharoptosis and levator function (LF), various surgical procedures, including levator resection, frontalis suspension, mullerectomy, and Fasanella-Servat are applied in the treatment [11-13]. Many ocular surgeons prefer levator resection in eyes with LF greater than 4 mm, and most of them believe that levator resection results in a better lid contour and position than frontalis suspension [14]. It has been reported that after the levator procedure, the mean corneal astigmatism decreased by 0.25 diopters (D), and contrast sensitivity improved significantly postoperatively [15, 16].

Levator resection surgery may affect corneal topography and higher-order aberrations (HOAs) since it eliminates the effect of the drooping upper eyelid on the ocular surface and corneal curvature. In particular, the impact of levator resection surgery on HOAs is not fully understood, and there are few studies on this subject in the literature. The present study evaluated changes in corneal topography and aberrometry in patients with acquired blepharoptosis after levator resection surgery.

METHODS

This prospective, interventional study evaluated 30 eyelids of 19 patients who underwent levator resection surgery for acquired blepharoptosis with fair and good LF at a single center between June 2023 and December 2024. The ptosis of all included patients was characterized by aponeurotic ptosis. The hospital's local ethics committee approved the study (number: 2011-KAEK-25 2023/05-14-31.05.2023). The study adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from each patient before surgery.

The patients underwent a routine ophthalmologic examination, including best corrected visual acuity (BCVA) (Snellen's chart and converted to the logarithm of the minimal angle of resolution (logMAR)), intraocular pressure (IOP), and biomicroscopic examination. Schirmer strips were used for the Schirmer I test in the outer third of the lower lid fornix without topical anesthesia, and the wet distance was measured after 5 minutes. It was considered abnormal if the measurements were ≤10 mm [17]. Tear breakup time (TBUT) was measured after using fluorescein dye as the time between the last blink and the first break in the dye on the cornea under biomicroscopic examination at x10 magnification with a cobalt blue filter. If the TBUT measurements were <5 s, it was interpreted as suggestive of dry eye [18].

Patients with gross eyelid pathologies other than acquired blepharoptosis, such as entropion or ectropion, previous corneal or eyelid surgery, pterygium, keratoconus, any corneal opacity, wearing contact lenses, strabismus, or syndromes such as Marcus Gunn jaw winking syndrome were excluded.

Blepharoptosis Evaluation

The position of the upper eyelid was evaluated in the primary gaze. Margin-reflex distance 1 (MRD1) is the distance between the upper eyelid margin and the corneal central light reflex in the primary position. Vertical fissure height (VFH) is the distance between the upper and lower lid margin. LF was determined by asking the patient to look up and down while pressing on the eyebrow and measuring the excursion of the upper eyelid margin. The distance ≤ 5 mm was classified as poor, 6-11 mm as fair, and ≥12 mm as good LF [19]. Levator resection was planned for patients with fair to good LF (>5 mm).

Corneal Topographic Measurements

Corneal topography and aberrometry were conducted using the Sirius device (CSO, Florence, Italy) before the surgery and 3 months postoperatively. Sirius imaging system combines a rotating Scheimpflug camera and Placido disk technology. Three precisely focused, centered, and aligned images were captured for each eye, and patients were instructed to blink twice to ensure a smooth corneal surface and reproducible measurement. To ensure uniformity in measurements, the upper eyelid was mechanically lifted in all eyes immediately before the aberrometry examination to visualize the centers of gravity. The same experienced technician took all measurements. To minimalize diurnal vaiations, all measurements were taken between 9 AM and 12 AM. The daytime to prevent diurnal variation. K1 (anterior corneal surface, flat keratometry), K2 (anterior corneal surface, steep keratometry), Kmean (anterior corneal surface, mean

keratometry), central corneal thickness (CCT), anterior chamber volume (ACV), anterior chamber depth (ACD), corneal astigmatism, axis of corneal astigmatism and total corneal optical aberration data root mean square (RMS)-HOA, RMS-Coma, RMS-Trefoil, Seconder astigmatism, RMS-Spherical aberration and RMS-Quadrafoil were compared preoperatively and at least 3 months postoperatively. Internal software automatically produces corneal wavefront data from aberrometry readings using Zernicke polynomials. The topography device produces total corneal aberrations based on four different pupil sizes (3, 5, 6, and 7 mm). For analysis standardization, all Zernicke coefficients and RMS values for 6-mm pupil size were evaluated for all eyes, and Zernicke coefficients higher than fifth order were not determined.

Surgical Technique

The same oculoplastic surgeon (D.D.) performed levator resection surgery under local anesthesia. The site of the proposed lid crease was marked. Lidocaine hydrochloride (20 mg/mL) and epinephrine (0.0125 mg/mL) were injected subcutaneously into the eyelid. After the skin and orbicularis oculi incision, the orbital septum was opened to expose preaponeurotic fat, a landmark for the levator muscle. Preaponeurotic fat retracted and levator muscle exposed. The levator muscle was separated from its insertion. Double-armed 6-0 coated polyglactin 910 (Vicryl) sutures passed through the tarsus. Eyelid position was evaluated intraoperatively. The measured excess part of the muscle was resected. The skin and orbicularis were closed.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 22 (IBM Corp., Armonk, NY, USA). Variables were examined using Shapiro-Wilk's test to determine distribution. The distribution of the data was normal. Continuous data are presented as mean ± standard deviation. Categorical characteristics are presented as numbers (%). The paired sample t-test was performed to compare preoperative and postoperative values, and P-value of <0.05 was considered statistically significant.

RESULTS

Thirty eyelids with acquired blepharoptosis from 19 patients (7 females and 12 males) with a mean age of 65.25±15.12 (range: 24-82) years were included in the study. The mean MRD1 of the patients was 0.69±0.90 mm (range: 0-3) preoperatively and 3.86±1.23 (range: 3-7) mm postoperatively (P<0.001). The mean VFH was 6.57±2.74 (range: 3-12) mm preoperatively and 10.33±2.45 mm (range: 6-17) postoperatively (P<0.001). The LF of the patients were 10.68±3.85 mm (range: 6-17) preoperatively and 14.01±0.11 mm (range: 7-20) postoperatively (P=0.045). Preoperative BCVA (logMAR) was 0.187±0.508 (range: 0-0.096), and postoperative BCVA (logMAR) was 0.141±0.602 (range: 0-0.070) (P=0.652).

The patients' mean Schirmer I test results were 14.95±8.07 mm (range: 10-20) preoperatively and 15.65±6.65 mm (range: 10-14) postoperatively

Table 1. Topographic data in the preoperative and postoperative 3-month

	Preoperative	Postoperative	P value
Flattest keratometry (K1) (D)	43.10±1.47	42.97±1.47	0.585
Steepest keratometry (K2) (D)	46.21±5.02	44.58±2.11	**0.046**
Mean keratometry (Kmean) (D)	44.44±2.45	43.73±1.37	0.122
Corneal astigmatism (D)	2.98±0.61	1.59±1.50	**0.034**
Axis of corneal astigmatism	74.50±61.76	82.83±62.80	0.548
Central corneal thickness (µm)	533.80±51.66	528.15±52.43	0.350
Anterior chamber volume (mm^3)	137.32±47.65	139.72±46.44	0.679
Anterior chamber depth (mm)	2.98±0.59	2.99±0.58	0.747

Data are shown as mean±standard deviation. D=Diopter.
Paired sample t-test, P<0.05 statistically significant.

Table 2. Corneal aberration data in the preoperative and postoperative 3-month

	Preoperative	Postoperative	P value
RMS-HOA	2.271±0.815	1.241±0.591	**<0.001**
RMS-Coma (Z_3^1)	2.941±0.731	0.424±0.642	**<0.001**
RMS-Trefoil (Z_3^3)	2.054±1.425	0.583±1.265	**0.005**
Seconder Astigmatism	0.768±1.852	0.284±0.915	0.345
RMS-Spherical aberration (Z_4^0)	0.510±0.835	0.365±0.511	0.255
RMS-Quadrafoil (Z_4^4)	1.928±5.371	1.549±1.536	0.715

Data are shown as mean±standard deviation. RMS=Root mean square, HOA=High-order aberrations, Paired sample t-test, P<0.05 statistically significant.

(P=0.405). The preoperative mean TBUT was 6.76±4.63 s (6-15), and the postoperative mean TBUT was 7.88±6.75 s (range: 6-16) (P=0.554).

Topographic data in the preoperative period and in the postoperative 3rd month are presented in Table 1. There were no statistically significant differences between the preoperative and postoperative values of K1 (43.10±1.47 and 42.97±1.47, respectively; P=0.585), K mean (44.44±2.45 and 43.73±1.37, respectively; P=0.122), axis of corneal astigmatism (74.50±61.76 and 82.83±62.80, respectively; P=0.548), CCT (533.80±51.66 and 528.15±52.43, respectively; P=0.350), ACD (2.98±0.59 and 2.99±0.58, respectively; P=0.747) and ACV (137.32±47.65 and 139.72±46.44 mm3, respectively; P=0.679) parameters. While preoperative K2 was 46.21±5.02, the postoperative K2 was 44.58±2.11 (P=0.046). Preoperative corneal astigmatism was 2.98±0.61, and postoperative corneal astigmatism was 1.59±1.50 (p=0.034).

Wavefront aberration data for the total corneal surface in the preoperative period and in the postoperative 3rd month are presented in Table 2 and Fig. 1. The RMS-HOA in the 6 mm optical zone was 2.271±0.815 µm, which decreased significantly to 1.241±0.591 µm (P<0.001). The RMS-Coma (Z_3^1) was 2.941±0.731 µm, which significantly reduced to 0.424±0.642 µm (P<0.001). While preoperative RMS-Trefoil (Z_3^3) was 2.054±1.425 µm, postoperative RMS-Trefoil (Z_3^3) was 0.583±1.265 µm (P=0.005). Preoperative and postoperative values of the seconder astigmatism (P=0.345), RMS-spherical aberration (Z_4^0) (P=0.255), and RMS-Quadrafoil (Z_4^4) (P=0.715) values were found similar.

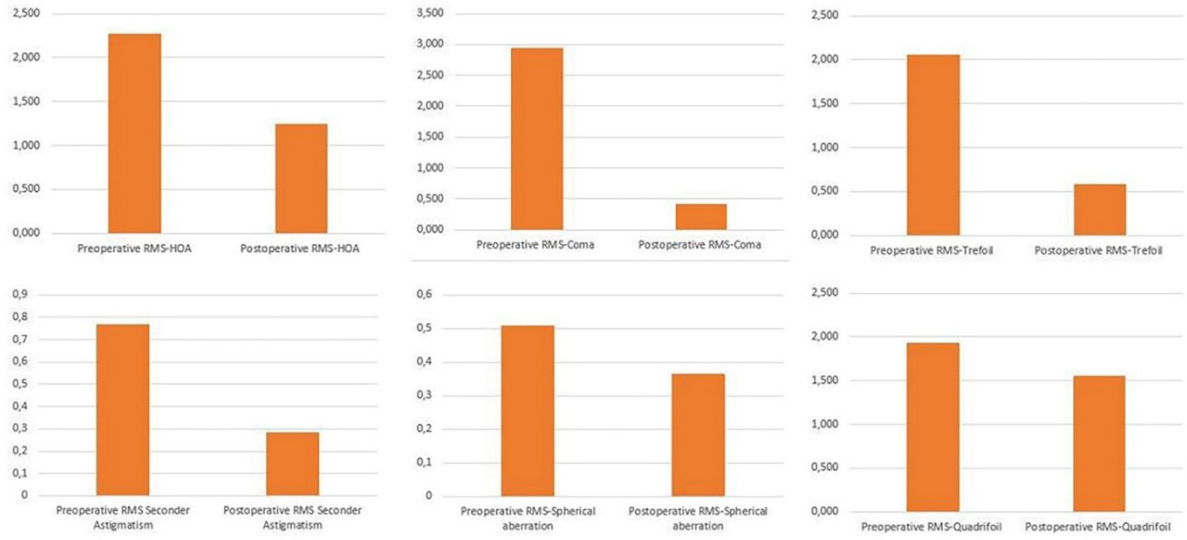

Fig. 1. Changes in corneal HOAs postoperatively. (RMS=Root mean square, HOA=High-order aberrations)

DISCUSSION

Levator resection surgery may improve visual function by removing the eyelid covering the pupil and changing corneal shapes [20]. It may modify the pressure on the opposing cornea and alter preexisting corneal curvature. This study investigated the effects of levator resection surgery on corneal topography in patients with acquired blepharoptosis. Cadera *et al*. [21] found that 36% of the study eyes' astigmatism changed by more than 0.75 D. Their results were similar for both fascia lata sling and levator resection [21]. Garima *et al*. [22] reported that the mean preoperative astigmatism was 1.28 D while the mean postoperative astigmatism was 1.71 D. Another study showed an average decrease of 0.18 D in astigmatism after congenital ptosis surgery [23]. This study found that postoperative corneal astigmatism decreased statistically significantly by an average of 1.39 D. In addition, it was observed that both K1 (from 43.10±1.47 to 42.97±1.47) and K2 (from 46.21±5.02 to 44.58±2.11) decreased postoperatively. The decrease in K2 was statistically significant. Our results matched the results of Islam *et al*. [24] found that K1 decreased from 43.00±1.28 preoperatively to 42.88±1.37 postoperative, and K2 decreased from 44.11±1.22 preoperatively to 43.99±1.44 postoperative. In another study, K1 and K2 changes in the 1st and 3rd months after ptosis surgery were not found to be significant [25]. These heterogeneous results of ptosis surgery on the cornea may depend on the type of topography devices used, the age of the patients (congenital or acquired), different races (eyelid morphology), and different follow-up periods.

Third-order and above aberrations are defined as RMS-HOAs. HOAs are an index of visual quality, and their reduction increases contrast sensitivity [26]. The anterior corneal surface is an essential contributor to the total HOAs of the eye. The impact on the corneal shape of the eyelid is mainly exerted on the anterior ocular surface. Shen *et al*. [27] reported that both the vertical coma and the vertical trefoil of the anterior corneal HOAs showed a significant difference between the ptosis and control groups. The upper eyelid pressure exerted on the cornea in a vertical direction is the likely optical explanation for the significant increase in vertical corneal aberrations since the upper eyelid drops. At the end of this study, it was observed that RMS-HOA, RMS-Coma, RMS-Trefoil, secondary astigmatism, RMS-Spherical aberration, and RMS-Quadrafoil decreased in the 3rd postoperative month. However, the decreases in RMS-HOA, RMS-Coma, and RMS-Trefoil were statistically significant. Safari *et al*. [28] reported that ptosis surgery for congenital upper eyelid ptosis corrected vertical coma in aberrometry, and as corneal astigmatism is > 1D, postoperative aberrometric changes are more pronounced. Han *et al*. [29] reported that third-order and coma-like aberrations were significantly reduced in patients who underwent levator resection. As a result, levator resection surgery may positively affect the quality of vision by reducing HOAs.

Upper eyelid surgery may cause postoperative dry eye symptoms by affecting meibomian, lacrimal and auxiliary tear glands, and orbicularis muscle by negatively impacting tear production. However, this effect has been shown to disappear within a few days [30]. For longer follow-ups, postoperative blinking recovery and eye dryness reduction may also improve postoperative HOAs. In this study, the postoperative Schirmer I test and TBUT increased slightly, but this increase was not statistically significant.

Limitations

The study's strengths are that it is prospective and examines dry eye parameters to observe the effect of aberrations. Its limitations are that it is a single-center study with a small sample size and a short follow-up period. Studies with larger patient groups and longer follow-up periods are needed.

CONCLUSION

Levator resection surgery reduced K2, corneal astigmatism, RMS-HOA, RMS-Coma, and RMS-Trefoil values in the postoperative 3rd-month.

Ethical statement

Consent was obtained from the patient. Ethics committee approval (number: 2011-KAEK-25 2023/05-14-31.05.2023) was obtained from the Bursa Yuksek Ihtisas Training and Research Hospital's local ethics committee.

Authors' Contribution

Study Conception: ASI, DD; Study Design: ASI,

MY; Supervision: DD; Funding: ASI; Materials: MY; Data Collection and/or Processing: MY; Statistical Analysis and/or Data Interpretation: ASI; Literature Review: DD; Manuscript Preparation: ASI and Critical Review: DD.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Correlation of radiological and histopathological findings in the diagnosis of benign bone tumors

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ABSTRACT

Objectives: Diagnosis of benign bone tumors is one of the diagnostic questions in the clinical practice which has an impact on the patient's quality of life. The work aimed to define the radiographic and histologic complementary diagnosis for benign bone tumors.

Methods: The present cross-sectional study included one hundred and forty-two patients with benign bone and soft tissue tumors referred to and followed up in the Adana Seyhan Hospital over a study period of 2010 to 2023. Patients were categorized based on the tumor type and radiological imaging was done through X-ray, Computed Tomography (CT), and Magnetic Resonance Imaging (MRI) scans. These results were then compared to histopathologic outcomes. Diagnostic indices such as the percentage accuracy, sensitivity, specificity, and positive and negative predictive values were estimated.

Results: In the study, 43.7% of the tumors were cartilaginous. MRI had the highest diagnostic accuracy (sensitivity of 96.9%, specificity of 83.3%, $P<0.05$). X-ray showed sensitivity of 90.8% and specificity of 66.7%, while CT showed sensitivity of 92.3% and specificity of 58.3%. A strong correlation was observed between radiologic and histopathologic findings ($r=0.87$, $P<0.001$).

Conclusions: Out of the histopathological features, there is a closely related association between the radiological and histopathological appearances in the diagnosis of benign bone tumors. Magnetic Resonance Imaging appears to be the only imaging modality with high accuracy of diagnosis. The concomitant interpretation of radiologic and histopathologic features allows for a considerable enhancement in diagnostic specificity.

Keywords: Benign bone tumors, radiological diagnosis, histopathological correlation

Benign bone tumors are those tumors that develop in the bones and do not display any malignant characteristics. Generally, these tumors are benign and slow-growing, with a lack of invasive behavior [1]. However, they can precipitate clinically relevant issues, for example, pain, edema, and pathologic fracture based on the area of involvement [2]. Therefore, it is essential to address the various challenges associated with diagnosing and treating benign bone tumors, as this impacts the overall well-being of affected patients and may subject them to unnecessary aggressive therapies [3]. Hence, early and correct identification of benign bone tumors is significant [4].

Radiography, Computed Tomography (CT) scans, and Magnetic Resonance Imaging (MRI) serve as important imaging techniques for the diagnosis of benign

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bone tumors. However, some benign lesions may present with radiological features that may mimic those of malignant lesions, leading to misdiagnosis [5]. Histopathologic examination is considered the gold standard in diagnosing these lesions. Nevertheless, the radiological and pathological findings are often inconsistent with each other [6]. Hence, it is necessary to assess the correlation between radiological assessment and histomorphological analysis of biopsied tissue to systematically analyze benign bone tumors.

The first research question of this study is therefore as follows: Is there a correlation between radiological and histopathological diagnosis of benign bone tumors? Supporting hypotheses are as follows: (1) For 208 patients, radiologic findings correlated with histopathologic diagnosis show that the method has high sensitivity and specificity. (2) Some specific radiologic features of a tumor may suggest one histopathologic subtype or another. (3) This may enhance radiologic and histopathologic correlation for heightened diagnostic performance.

Few articles can be found in the literature that focus on detailed investigations of the correlation of radiological and histopathological appearances of benign bone tumors [7]. Particularly in Turkey, there is no large-scale study on this subject. The aim of the current study is to address this lack of research and provide new insights for clinical practices.

This study investigates the relationship between the radiologic and histopathological diagnosis of benign bone tumors for improving diagnostic accuracy in pathology [8]. Furthermore, the correlation between radiological and histopathological findings of different subtypes of benign bone tumors will be elucidated in detail, and a flowchart is planned to be designed to assist clinicians during the diagnosis.

METHODS

Cross-sectional study intended to examine the relationship between radiological and histopathological characteristics in benign bone and soft tissue tumors. Patients monitored from 2010 to 2023 at the Orthopedics and Traumatology Clinic of Adana Seyhan Hospital were analyzed. Patients diagnosed with benign bone and soft tissue tumors were enrolled at our center. Some of the most widely used equipment are X-ray, CT, and MRI systems.

Study Population

The age of patients ranged from 18 to 75 years, with a balanced distribution between male and female participants. Patient selection was carefully controlled for demographic factors to ensure representative sampling across different socioeconomic groups. For inclusion in the study, patients needed to be 18 years or older, have a confirmed diagnosis of benign bone or soft tissue tumors, have complete radiologic and histopathological data available, and provide written informed consent. We excluded patients who had malignant tumors, were under 18 years of age, had incomplete radiological or histopathological data, were pregnant, had previous surgical intervention at the tumor site, or had concurrent systemic diseases affecting bone metabolism.

This cross-sectional study was conducted at the participants were patients registered in Adana Seyhan Hospital. For the study material, all relevant radiological imaging techniques necessary for tumor diagnosis were applied according to standard protocols. Participants All patients were selected according to the aims and hypotheses of this clinical study, as long as complete radiologic and histopathologic data was available. To improve the scientific validity of the study, selection criteria were carefully established. Since this was a cross-sectional study, it was possible to evaluate tumor classification radiological and histopathological data during that period. Randomization of patients and blinding were used factors to reduce bias. This study was conducted on participants recruited randomly and to prevent bias, the data during analysis was blinded.

The present research conformed to the guidelines of the Declaration of Helsinki of 1964. The current research received clearance from the Adana City Clinical Research Ethics Committee. Accordingly, written consent was obtained from the participants, and the ethics committee identification number for the study is 129. Meeting Number: 4, Date: 15.08.2024.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as means and stan-

dard deviations for continuous variables and as frequencies and percentages for categorical variables. The diagnostic performance evaluation included calculations of sensitivity, specificity, positive and negative predictive values, and overall diagnostic accuracy. We performed Receiver Operating Characteristic (ROC) curve analysis and calculated the Area Under the Curve (AUC) values. The relationship between radiological and histopathological findings was assessed using Spearman's rank correlation coefficient, while inter-observer reliability was evaluated using Cohen's kappa coefficient. Missing data were handled using multiple imputation techniques. Statistical significance was set at $P<0.05$ for all two-tailed tests, and Bonferroni correction was applied for multiple comparisons to control for Type I error.

RESULTS

Among the 142 benign bone and soft tissue tumors analyzed in our study, cartilaginous tumors were the predominant type, comprising 43.7% of all cases. Of these, osteochondroma was the most common subtype (26.8%), followed by enchondroma (14.8%). Osteogenic tumors and vascular tumors represented 12.7% and 8.5% of cases, respectively. Various other tumor types constituted the remaining 30.2% of the total cases (Table 1).

When comparing methodical radiological diagnostic methods and histological diagnosis, it was clear that among the benign tumors, X-ray which is usually a sensitive test (90.8%) had its specificity at 66.7%. CT was able to identify an average of 92.3% correctly positive cases while reporting 58% correctly negative. It appeared that sensitivity analysis pointed out MRI having the greatest diagnostic sensitivity of 96%. Specificity also reported good range at 83% while sensitivity stood at 90%. It would therefore seem feasible that each of the imaging methods is capable of characterizing and positioning benign neoplasms appropriately. However, in the focused study concerning benign neoplasms, MRI turned out to be the most sensitive technique (Table 2).

As per the findings of the study, the X-ray imaging technique demonstrated efficacy in diagnosing a benign bone and soft tissue tumor with a sensitivity and specificity of 90.8% and 66.7% respectively, however, it was established that the imaging technique has the risk of underutilizing benign tumors with a negative predictive value of 40.0%. The sensitivity analysis showed that CT had a sensitivity of 92.3%, slightly higher than that of the X-ray. The analysis of specific lesion types revealed that certain features were associated with varying diagnostic accuracy. For example, parietal lesions, perilesional lesions, and insular cortex lesions were associated with a sensitivity of 73% and were likely to misdiagnose benign tumors with a specificity of 58.3%. The most notable containing 96% sensitivity was MRI, which made it the most useful in diagnosing the disease over other diagnostic modalities. MRI showed a positive predictive value of 90% while the negative predictive value was 39%, and the overall accuracy was 87.3%, making it more effective in identifying patients with benign lesions with a sensitivity of 71% and a negative predictive value of 71.4%. The degree of diagnostic capacity of MRI was also established with a positive predictive value of

Table 1. Frequency of benign bone and soft tissue tumors

Histology	n	%
Cartilaginous tumors	62	43.7
Osteochondroma	38	26.8
Enchondroma	21	14.8
Chondromyxoid fibroma	3	2.1
Osteogenic tumors	18	12.7
Osteoid osteoma	11	7.7
Osteoblastoma	7	5.0
Vascular tumors	12	8.5
Hemangioma	12	8.5
Lipogenic tumors	4	2.8
Lipoma	4	2.8
Fibrogenic tumors	3	2.1
Desmoplastic fibroma	3	2.1
Miscellaneous tumors	43	30.2
Aneurysmal bone cyst	15	10.6
Histiocytosis X	5	3.5
Simple cyst	14	9.8
Non-ossifying fibroma	9	6.3

Histiocytosis X=Traditional name for Langerhans cell histiocytosis

Table 2. Comparing the radiological diagnoses with histological diagnoses across X-ray, CT, and MRI

Radiological diagnosis	X-Ray	CT	MRI
Benign tumor	118 (TP), 4 (FP)	120 (TP), 5 (FP)	126 (TP), 2 (FP)
Suspicious lesion	12 (FN), 8 (TN)	10 (FN), 7 (TN)	4 (FN), 10 (TN)
Total	130, 12	130, 12	130, 12

TP=true positive, FP=false positive, TN=true negative, FN=false negative, CT=computed tomography, MRI=magnetic resonance imaging

98.4% (Table 3).

These results were supported by other findings when it came to diagnostic performance criteria and similar F1 scores of X-ray, CT, and MRI of 93.7%, 94.1%, and 97.6%, respectively. The smallest percentage of false positives was 16.7% for MRI, 33.3% for CT, and 41.9% for X-ray, as demonstrated in Fig. 1. In addition, radiological imaging modalities were correlated with histopathological examination to illustrate the applicability of each approach in disclosing numerous peculiarities of benign bone tumors (Fig. 2 and Fig. 3).

DISCUSSION

This investigation aimed to explore the relationship between radiographic and histologic features of benign bone neoplasms while providing insights for more accurate diagnosis. Our findings revealed a strong correlation between radiological characteristics and histopathologic diagnosis in benign bone tumor cases. It was observed that radiologic findings are sensitive and specific in indicating the histopathologic findings. Particular radiologic features were noticed to suggest some of the histopathologic subtypes of the tumor. In addition, this approach of integrating radiologic with histopathologic results in determining the benign bone tumor diagnosis was significantly effective. These results demonstrate that combining both approaches is crucial for the accurate diagnosis of benign bone tumors, and the findings presented here will serve as a valuable resource for clinicians.

According to our study, the sensitivity of MRI is 96 percent. Specificity was 83%, the sensitivity of the test was 9.3% in the diagnosis of benign bone tumors, and similar findings were observed in other studies in the literature. Schenker *et al*. [9] also observed a high sensitivity of MRI in the diagnosis of epithelioid hemangioma. X-ray imaging showed 90.8% sensitivity

Table 3. Advanced diagnostic metrics for X-ray, CT, and MRI

Metric	X-Ray (%)	CT (%)	MRI (%)
Sensitivity	90.8	92.3	96.9
Specificity	66.7	58.3	83.3
Diagnostic Accuracy	88.7	89.4	95.8
Positive Predictive Value	96.7	96.0	98.4
Negative Predictive Value	40.0	41.2	71.4
F1 Score	93.7	94.1	97.6
False Positive Rate	33.3	41.7	16.7
False Negative Rate	9.2	7.7	3.1
AUC (ROC Curve)	0.85	0.88	0.92

CT=computed tomography, MRI=magnetic resonance imaging, AUC=ROC curve, area under the receiver operating characteristic curve, F1 score=harmonic mean of precision and recall, X-ray=x-radiation

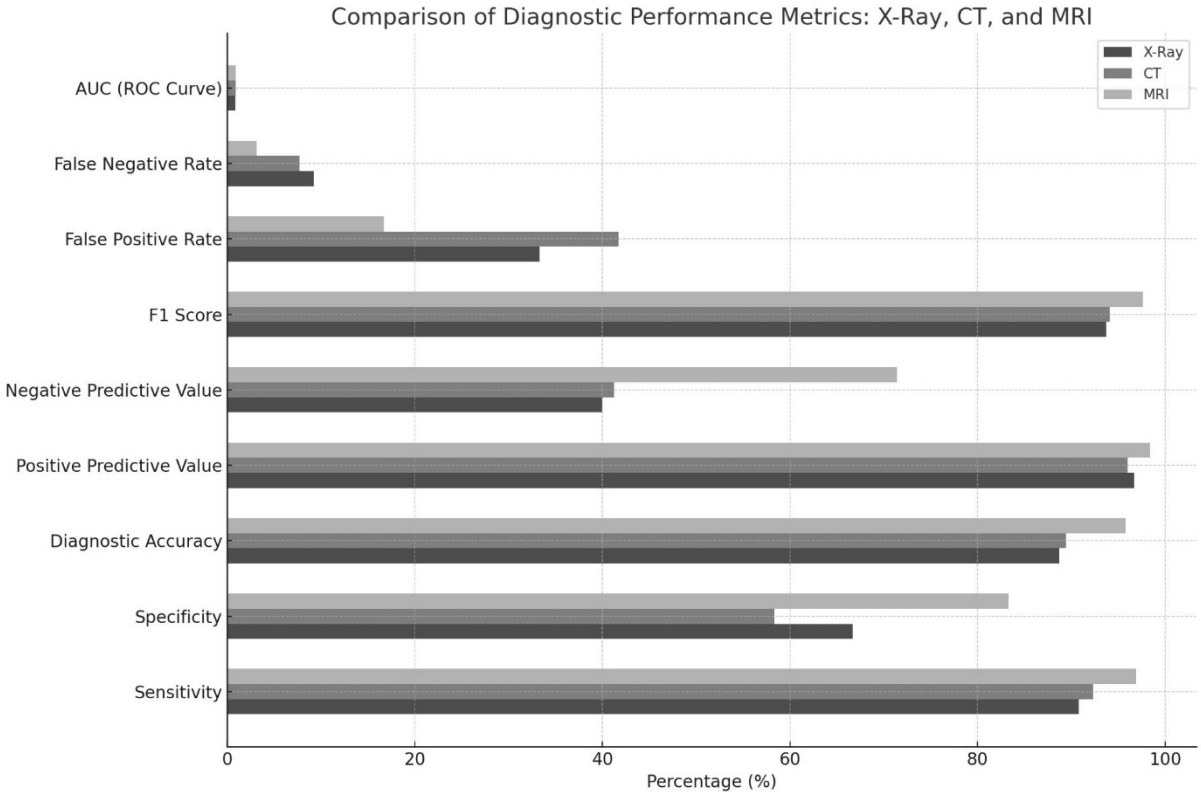

Fig. 1. Comparison of diagnostic performance metrics: X-Ray, CT, and MRI.

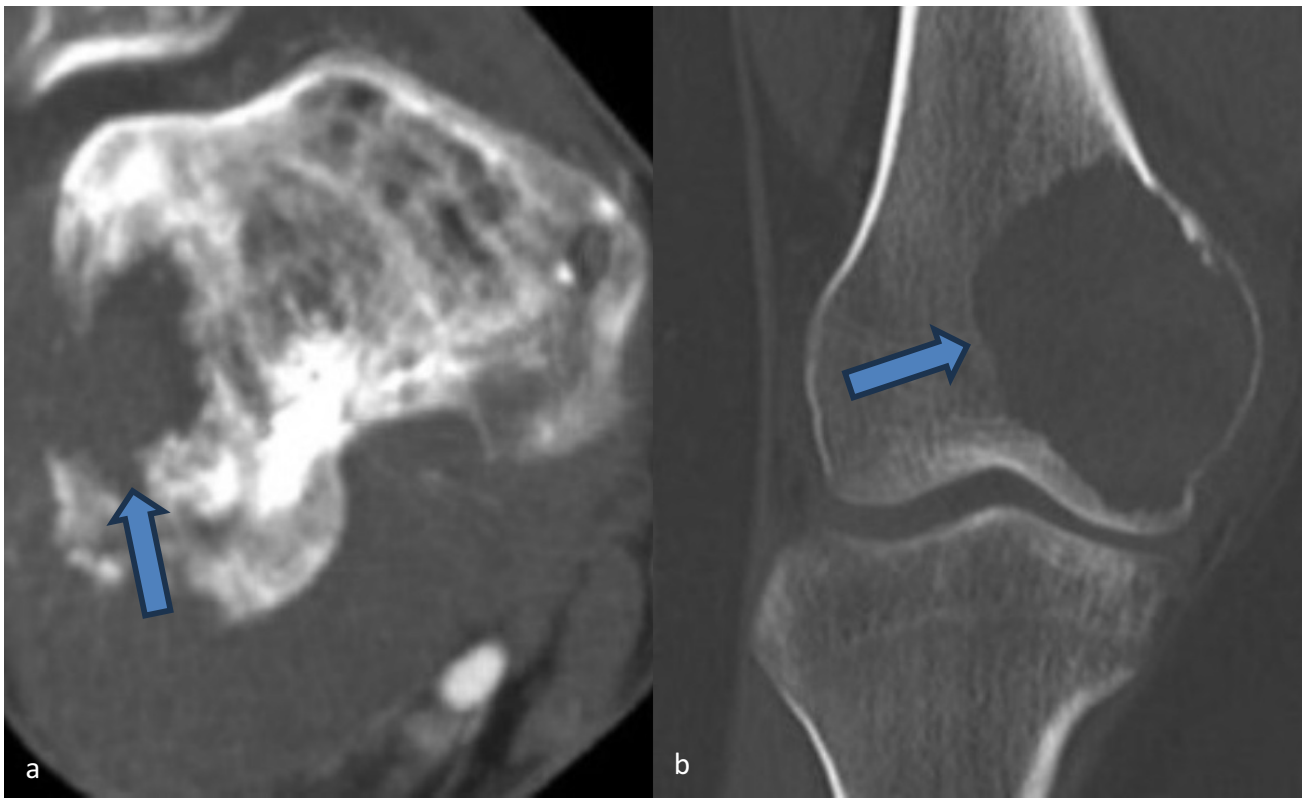

Fig. 2. Aneurysmal bone cyst. a) Axial CT, image showing the expansile lytic lesion, b) Sagittal CT image demonstrating the extent of the lesion.

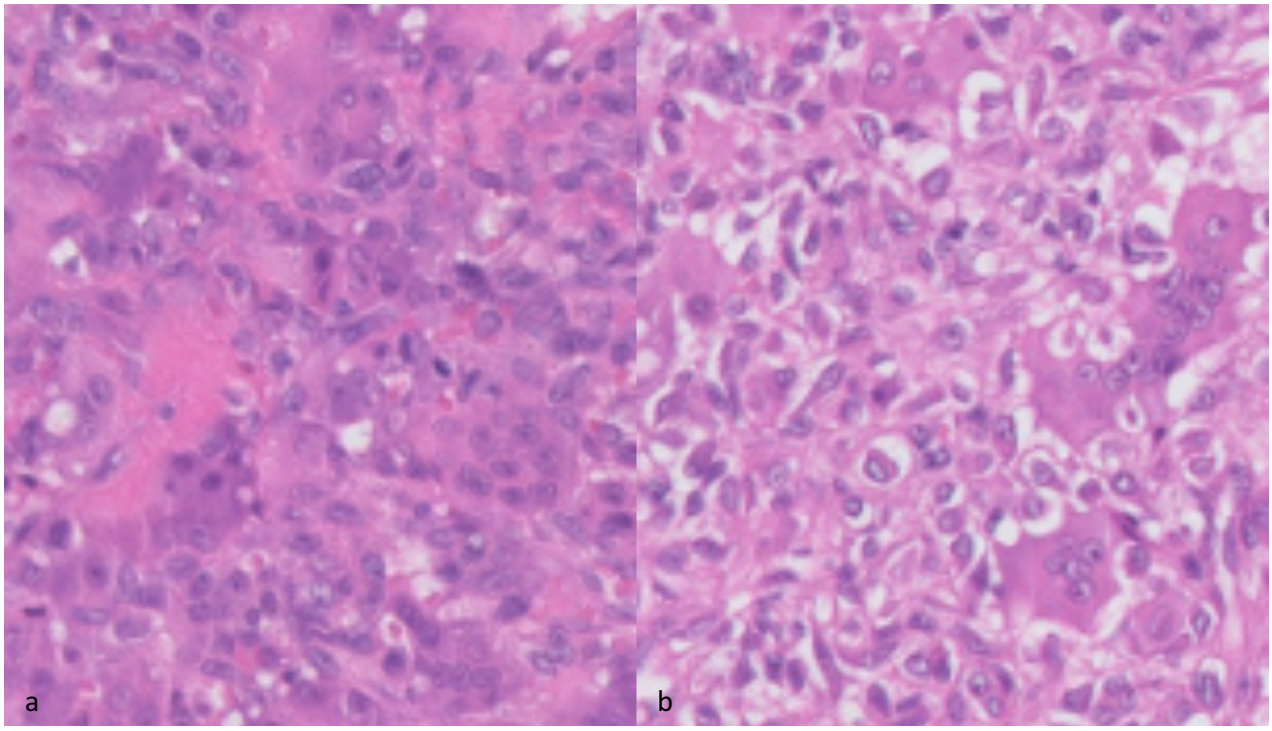

Fig. 3. Giant cell tumor. a) Multinucleated giant cells, H&E stain; ×200, b) Detailed cellular morphology, H&E stain; ×400.

and 66.7% specificity in our study with results similar to those found in the CBCT study by Gröbe *et al*. [10]. The sensitivity of 92.3% and specificity of 58.3% reported in this study are in agreement with those recorded in the literature regarding the effectiveness of methods used in the early detection of oral cavity cancers and highlight the merits of the existing screening procedures [11]. Moreover, it should be noted that the results of our study, which demonstrated a strong correlation between radiological and pathological features of the disease, were also reported by Meyer *et al*. in the cohort of patients diagnosed with systemic mastocytosis [12].

In our study, the most frequently observed subtypes during the histopathological assessment of benign bone tumors were in agreement with the literature review as well. Similar to the study by Collins *et al*. [13], ossifying fibroma cases occupied an important place in our study. As highlighted in the study by Gupta *et al*. [14], the critical importance of histopathological examination in tumor staging and grading was confirmed in our study. As observed in the study by Hingsammer *et al*. [15], a strong correlation was identified between histopathologic findings and radiologic findings in our study. Furthermore, as emphasized in the study by Pereira *et al*. [16] on fibrous dysplasia, the importance of the correct definition of histopathologic subtypes in terms of clinical management was demonstrated in our study.

In this regard, a uniform radiological and histopathological evaluation of benign bone lesions was rather satisfactorily presented in our study. This conclusion is also found in similar studies in the literature. Vadalà *et al*. [17] emphasized that radiological and histopathological findings were complementary to each other. Our study pointed out that the combination of radiological and histopathological correlation led to greater diagnostic efficiency, similar to the findings by Lennerås *et al*. [18]. Furthermore, as observed in the study by Zhou *et al*. [19], our study revealed that specific radiologic features may indicate certain histopathologic subtypes. The novel feature of this study is that it advances the understanding of bone autograft sterilization methods by integrating radiological, biomechanical, and histopathological evaluations, showcasing how these approaches aid in determining the most effective techniques for limb salvage surgery [20].

Some of the individual radiologic features were found intently in that they corresponded to certain histopathologic subtypes. For instance, the "owl-like" appearance that is observed in patients with osteoid osteoma was noted in the imaging studies, and even histopathological results corroborated it. The need of radiologic-histopathologic correlation is also supported by the finding of the study conducted by Chaudhary *et al*. [21]. The 'ground-glass' appearance is a characteristic radiological feature often observed in fibrous dysplasia, as highlighted in the context of sinonasal diseases and their radiological evaluation in this study [22] as well as in our study. The location at the epiphysis and mode of calcification seen in cases of chondroblastoma in our study were comparable with those described by Buonomo *et al*. [23]. The unique contribution of our study to the literature is that it demonstrated in a larger patient population that the combined evaluation of radiologic and histopathologic findings increases diagnostic accuracy, as in the study by Seyedmajidi *et al*. [24].

Limitations

This study has a large patient sample, a thorough description of different radiological methods (X-ray, CT, and MRI), and a meticulous study of the histopathological data. Even with the said strengths, it should be noted that a limitation of this study is the fact that it is a single center and therefore the design itself may impose limitations on the generalizability of the findings. On the other hand, the limited amount of information for particular types of benign bone tumors which are uncommon may also be seen as a shortcoming. In practical applications of our study, it is shown that concerning the evaluation of suspicious lesions, MRI should always be used rather than other imaging modalities and that a combined assessment of imaging findings and histopathological results improves the accuracy of diagnosis. Therefore, a multidisciplinary approach to the diagnosis of benign bone tumors and close collaboration between radiologists and pathologists are recommended.

CONCLUSION

A high correlation between the histologic and the radiologic impression was achieved in the evaluation of benign skeletal neoplasia in this investigation. The study states that MRI was most effective as an imaging modality. It is basic knowledge that some imaging features are specific for certain histopathology. It has also been noted that the combination of Diagnostic Imaging and Diagnosis permits a better diagnosis. Considering these observations, a multidisciplinary approach is recommended in the diagnosis and treatment of benign bone tumors, in which all imaging techniques work closely with the pathology department.

Ethical statement

Approval of this study was obtained from the Adana City Hospital Clinical Research Ethics Committee with the ethical approval code issued for conducting research involving human participants (Number: 4, Date: 15.08.2024).

Authors' Contribution

Study Conception: BE; Study Design: BE; Supervision: SM; Funding: SM; Materials: BE; Data Collection and/or Processing: SM; Statistical Analysis and/or Data Interpretation: BE; Literature Review: BE; Manuscript Preparation: BE and Critical Review: SM.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Analysis of skin health management through telemedicine and mobile health in dermatology in the post-COVID era

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ABSTRACT

Mobile health has made significant strides in the field of tele-dermatology (TD) following the developments post the COVID-19 pandemic. The application of telemedicine and mobile health to dermatology holds the potential to enhance the quality of healthcare for citizens and streamline workflows in the healthcare domain, hence this subject is of great importance. This research encompasses the last three years. A comprehensive overview examining the opportunities, perspectives, and encountered challenges regarding the integration of TD with mHealth has been provided. The narrative review methodology is based on (I) conducting research via PubMed and Scopus, and (II) conducting compliance assessment using the proposed parameters. The outcome of the research indicates rapid progress in the integration of TD with mobile health during the COVID-19 pandemic. This integration has facilitated the monitoring of dermatological issues and allowed for remote specialist visits, thereby reducing face-to-face interactions. Artificial intelligence and mobile applications have empowered citizens to take a more active role in their own healthcare, which is distinct from other imaging areas where information exchange is limited only to professionals. Opportunities that TD can offer in the field of mobile health include enhancing service quality, increasing the efficiency of healthcare processes, reducing costs, and providing more accessible care. This is applicable not only to conditions like acne, vitiligo, psoriasis, and skin cancers but also to other conditions. Integration with artificial intelligence and augmented reality (AR), along with the use of wearable sensors, are expected as future developments. However, the integration of TD with mobile health brings along issues and challenges related to regulation, ethics, cybersecurity, data privacy, and device management. These issues, along with the involvement of citizens in the process, should be addressed by scientists and policymakers.

Keywords: Telemedicine, mobile health, dermatology, tele-dermatology

Telemedicine's application in dermatology, commonly termed tele-dermatology (TD), encompasses two distinct approaches: synchronous (real-time, RT) TD and asynchronous (store-and-forward, SaF) TD. The SaF model allows for asynchronous consultations between patients and dermatologists, effectively reducing wait times for appointments. Conversely, RT TD employs video conferencing for immediate patient-doctor interaction and remains a popular method in dermatology practice [1, 2].

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TD has witnessed significant growth since 1995, with an abundance of related literature. A specific search strategy conducted on PubMed revealed 1287 related articles, with 590 (45.8%) published post-January 2020, aligning with the COVID-19 pandemic. TD enhances the quality of healthcare services, positively impacting the healthcare system including patients, general practitioners, and specialists. This enhancement is evident in improved monitoring, treatment, and overall healthcare processes, contributing to increased satisfaction among all involved parties [3, 4].

The integration of mobile health (mHealth) with TD introduces a synergistic advancement in dermatology. TD, leveraging digital health solutions, can significantly reduce or eliminate the necessity of physical travel, delivering treatments directly to the patient's location. mHealth, through specific applications on smartphones or tablets, democratizes dermatological care, enabling users to manage their conditions via virtual consultations and self-care applications. This integration marks a departure from traditional digital imaging fields such as digital radiology and pathology [5, 6].

In addition to the opportunities and challenges seen in other digital imaging disciplines, this paper also explores unique prospects and challenges in the integration of mHealth with TD. This integration plays a pivotal role in reshaping dermatological practices and enhancing patient engagement, highlighting its significance in the field [7, 8].

The scholarly focus on this topic, especially against the backdrop of the mobile technology boom, is relatively recent, with literature available on PubMed dating back to 2012. The growing interest in this area aligns with the advancements in mobile technology.

The search strategy used in this study involved targeting both teledermatology and digital dermatology and their intersections with mobile health applications. The findings indicate that, as of the date of this research, 87 studies were identified, with 40 (45%) published since January 1, 2020, during the COVID-19 pandemic. This period has notably spurred innovation in biomedical technologies, including TD. This narrative review aims to provide an overview of the developments in TD and mHealth integration over the past three years, identifying opportunities, challenges, and offering guidance for clinicians, researchers, and policymakers. The specific objectives include assessing the evolution of studies in this field; evaluating the current state of TD and mHealth, highlighting their strengths and limitations; identifying potential benefits of integration such as improved diagnostic accuracy and patient outcomes; exploring challenges like data privacy and regulatory issues; and providing best practice recommendations for implementation in dermatology. The studies discussed offer insights into both research directions and indirectly highlight gaps and bottlenecks [9].

EMERGİNG TRENDS İN TELE-DERMATOLOGY AND MOBİLE HEALTH INTEGRATİON

Responding to the COVID-19 Pandemic

The burgeoning interest in tele-dermatology (TD) prior to the COVID-19 pandemic is well-documented through significant studies [10-19]. These studies reflect the maturity of this technology, transcending its nascent stage. Clark *et al*. [19], in a systematic review conducted at the end of 2018, underscored the global access to mobile phones (4–6 billion users) and posited TD as a viable tool for diagnosis and management in dermatology. They offered a thorough assessment of mobile phone technology's integration in dermatology, probing the accuracy and concordance of mobile TD compared to traditional face-to-face consultations for skin condition diagnoses. Done *et al*. [18] explored an interoperable informatics client-server system (VA Telederm) comprising a web server and client-accessing apps. VA Telederm, designed for integration into the US Veterans Health Administration's existing TD workflow, showcased the feasibility of using mobile technology for consultative store-and-forward dermatology in large healthcare organizations. Koh *et al*. [17] examined the potential of mobile TD in facilitating skin self-examinations (SSEs) and enhancing melanoma monitoring and detection. Their study evaluated consumer acceptability and expectations of a mobile health app designed for SSE instruction and consumer-performed mobile teledermoscopy. Silveira *et al*. [16] conducted a study in Brazil on a mobile application developed for aiding skin cancer diagnosis, demonstrating its potential and reliability. The study indicated its viability as an auxiliary option in regions with limited access to dermatology clinics. Akdeniz *et al*. [15] focused on encouraging primary

healthcare professionals to engage actively in early skin cancer diagnosis among nursing home residents. They emphasized the significance of integrating mHealth with TD, suggesting dermoscopy courses and web or smartphone-based applications to support healthcare professionals in early skin cancer detection. Shambi *et al*. [14] investigated acne apps, assessing their features and overall quality in facilitating clinical management. Their findings indicated the effectiveness of mobile acne apps in self-management and collaborative management of acne, despite variability in app quality and the absence of certain crucial features for effective clinical management. Marwaha *et al*. [13] evaluated the efficacy and value of TD compared to face-to-face workflows in diagnosing lesions. Their study, examining risks associated with biopsy and cancer diagnosis across different workflows, underscored the importance of mHealth implementation for TD effectiveness. Damsin *et al*. [12] provided a synthesis of the TeleSPOT project objectives, focused on early melanoma detection through TD in general practice. TeleSPOT utilized smartphone-based pigmented lesion diagnosis and an online taskforce to aid dermatologists in distinguishing suspect pigmented skin lesions. Tongde *et al*. [11] highlighted the growing integration of mobile apps in the medical field, with dermatology being no exception. They reviewed various types of dermatology apps, including those for TD, self-surveillance, disease guides, reference, dermoscopy, and others, analyzing their popularity in the Apple App Store.

THE UNPRECEDENTED IMPACT OF THE COVID-19 PANDEMİC

The Idea of the Overview

The last three years have witnessed a significant surge in interest in TD and its integration with mobile health (mHealth), largely due to the COVID-19 pandemic [10]. The pandemic has been a catalyst for TD's amalgamation with mHealth and artificial intelligence, influencing remote diagnoses of general skin pathologies and specific pathological conditions indicative of COVID-19.

The transfer of image detection tools into the hands of citizens, a necessity for protecting vulnerable groups and maintaining social distancing, has not completed the transition process. This shift has inevitably exposed critical issues, leading to a paradigm change in citizen–patient and doctor–specialist relationships, a contrast to the practices in teleradiology or telepathology. This new paradigm involves citizens as operators/technologists, raising significant implications including digital divide, privacy, data security, technology, standardization, ethics, and specific training of use. The integration of AI with patient-held apps has further broadened the scope of this field, prompting reflections by scholars, developers, and decision-makers. [20].

RESULTS

All studies passed the qualification step of Algorithm. The search yielded 40 relevant studies [21-60] since the onset of the COVID-19 pandemic.

The analysis categorized the contributions into various emerging fields of interest, including opportunities in TD and mHealth, development and testing methodologies, integration models, and challenges and bottlenecks. Some studies overlapped these categories, addressing multiple issues.

The categorization revealed specific fields of interest: opportunities in TD and mHealth, development and implementation methodologies, integration models, and identification of problems and bottlenecks.

Opportunities of TD and mHealth

Studies in this sector unanimously agreed on the promising prospects of tele-dermatology (TD) in mobile health (mHealth), emphasizing its role in enhancing overall service quality [21, 26, 27, 31, 33-35, 40-45, 48, 50-60]. Evidence suggests that TD and mHealth can improve care quality, healthcare processes, cost efficiency, and patient satisfaction, while reducing the stress on healthcare facilities. Specific studies have delved into various aspects, including potential bottlenecks, care models, and development requirements.

For instance, Gandhi *et al*. [21] highlighted a TD application's accuracy in diagnosing vitiligo. Handa *et al*. [42] assessed acceptance and opinions of TD during the COVID-19 pandemic, noting its effectiveness as an alternative to in-person visits. Hampton *et al*. [44] evaluated an app's usability for guiding skin care,

finding it user-friendly. Yotsu *et al*. [45] explored an app (eSkinHealth) for disease management in sub-Saharan Africa. Tognetti *et al*. [51] reviewed an AI-based TD service for melanoma screening, noting its potential for widespread use. Peracca *et al*. [52] examined the feasibility and usage frequency of mobile mHealth tools in TD. The TELESPOT project [57] in Belgium developed a smartphone-based dermoscopy app with success in user-friendliness and effectiveness. Sondermann *et al*. [59] showed that TD and mHealth successfully reduced spatial and temporal barriers in dermatology care.

Development, Implementation, Testing, and Shared Methodologies

Five studies focused on design specifics and procedures in this field. Ritvi *et al*. [27] detailed a smartphone app in Norway for referring skin lesion cases to dermatologists, reducing unnecessary specialist consultations. Abbott *et al*. [43] proposed a guideline for capturing high-quality clinical images. Po Harvey Chin [50] developed a mHealth tool for remote self-assessment of digital ulcers. Huang *et al*. [55, 56] investigated the Nuru-goTM Derma device, a cost-effective tool for preliminary triage and remote diagnosis through teledermoscopy.

TD, mHealth, and the Integration Models

Six studies concentrated on the models of TD and mHealth and their implications. Trinh *et al*. [53] assessed organizational readiness for implementing a patient-facing mobile TD app. Veronese *et al*. [54] piloted a care model for elderly patients in senior living communities. Kho *et al*. [41] explored different business models in TD and mHealth. Yadav *et al*. [35] assessed patient satisfaction with a hybrid TD model during the pandemic. Johnson *et al*. [26] identified barriers and facilitators in monitoring low-risk skin lesions. Kling *et al*. [34] found that TD and mHealth increased follow-up care capacity but did not significantly improve care transition timeliness.

Problems and Bottlenecks

Six studies tackled the challenges in TD and mHealth. Lull *et al*. [31] evaluated German apps for psoriasis, emphasizing the importance of involving patients in app development. Han *et al*. [48] focused on privacy and security in healthcare, proposing a zero-watermarking scheme. Vestergard *et al*. [58] discussed the accuracy of TD in skin cancer recognition. Cronin *et al*. [60] reported how camera distance and angle can affect color accuracy in medical photography. Sun *et al*. [33, 40] highlighted issues in application standards and consent procedures in digital skin imaging.

Data Synthesis from the Observational Studies

Three observational studies [39, 46, 47] revealed various insights. Mostafa and Hegazy [39] showed high satisfaction and efficiency in using TD and mHealth in Cairo, Egypt. Dusendang *et al*. [46] compared different TD workflows and their impact on dermatology service utilization. Gimeno-Vicente *et al*. [47] assessed the emotional impact of WhatsApp consultations on dermatologists, noting negative effects and a preference for moderated use.

In summary, these sections synthesize a wealth of findings in TD and mHealth, covering opportunities, developmental methodologies, integration models, and identified challenges, thereby providing a comprehensive view of the current state and future potential in this evolving field.

Data Synthesis from Randomized Clinical Trials

The overview returned two randomized clinical trials (RCTs) [37, 49]. Domogalla *et al*. [37] highlighted the use of a disease management smartphone app to improve the mental health of patients with psoriasis. The study found that the app was able to induce a significant reduction in HADS-Depression scores, although further research is needed to assess the app's use frequency and its relationship with the patient outcomes. Zhang *et al*. [49] focused on the development of an image-AI-based system called Skin-Teller App to assess the severity of psoriasis. The study found that the model outperformed the average performance of 43 experienced dermatologists, with a 33.2% performance gain in the overall PASI score. The app has been used in multiple hospitals and has been confirmed to be an excellent alternative for accurate assessment by dermatologists and chronic disease self-management in patients with psoriasis.

Considered together, these two studies showed that the TD integration with mHealth:

•Improved access to healthcare: TD and mHealth can improve access to healthcare services for patients who may face geographic, financial, or other barriers

to in-person appointments.

•Increased efficiency: TD and mHealth can help to reduce wait times and streamline the triage and treatment processes.

•Better patient outcomes: TD and mHealth can lead to better patient outcomes, such as more accurate diagnoses and improved management of chronic skin conditions.

•Enhanced patient engagement: TD and mHealth can empower patients to take a more active role in their healthcare by providing them with tools and resources to better manage their skin health.

•Improved mental health: The use of disease management smartphone apps may improve the mental health of people with psoriasis.

Data Synthesis from the Reviews

The reviews covered various aspects of the integration of TD and mHealth, sometimes in the context of the COVID-19 [22-25, 28-30, 32]. Glines *et al*. [22] studied the impact of technology, particularly imaging technologies, on the field of dermatology. The article discussed the use of TD and mHealth to improve diagnostic accuracy and provide access to dermatologic evaluations for underserved communities and those in rural settings. It was suggested that incorporating digital dermatology into clinical practice required legal frameworks to be addressed and reimbursement policies to be updated in order to benefit patient care. Petracca *et al*. [23] evaluated the implementation of a mobile TD app at three Department of Veterans Affairs sites using a properly designed approach. The study evaluated the organizational readiness for change (ORC) and identified enablers, obstacles, and factors affecting its implementation. The results showed a high readiness for change, with an ORC score of 4.2 out of 5. The study by Marasca *et al*. [24] was a review of the scientific literature on the applications of TD and mHealth for inflammatory skin diseases. The study found that TD and mHealth have been demonstrated to increase access to resources in the health domain, improving the access to specific dermatological care for people living in remote areas. Kevderiane *et al*. [25] reviewed and discussed the use of TD and mHealth in the care of allergic diseases of the skin. This was studied both in everyday life and in the context of COVID-19. The review discussed the TD and mHealth applications and their practical benefits for clinical trials. The study highlighted a high level of patient satisfaction. However, the review also discussed some of the limitations and challenges of these technologies. Havelin *et al*. [28] specifically reviewed the use of TD and mHealth, including AI, in managing psoriasis. The authors conducted literature searches and reviewed research publications linked to apps containing the keyword "psoriasis" to answer key questions relating to this field. In addition, they searched for apps dedicated to "psoriasis" on the analytic website www.appannie.com and reviewed research publications linked to these apps. Lee *et al*. [29] discussed how the COVID-19 pandemic affected dermatology and how TD became a popular alternative to in-person visits. Mobile TD, which allows patients to monitor and forward images of suspicious skin lesions to dermatologists for remote medical evaluation, was shown to represent a useful communication tool between medical practitioners and patients. AI technology was also used to assess clinical images for skin cancer. The authors concluded that there is a future for TD and mHealth in skin cancer detection, based on the incorporation of direct-to-consumer mobile dermoscopy with mole-scanning artificial intelligence. Perrone *et al*. [30] discussed the various areas of telemedicine that have evolved during the COVID-19 pandemic, including teleradiology, telecardiology, and TD and mHealth. The latter has enabled the early identification of diseases through diagnoses of cutaneous signs. AI has also enabled the early diagnosis and monitoring of infections. Greis *et al*. [36] highlighted the advantages of mHealth and AI in dermatology, particularly in African countries with limited medical care and long distances between patients and physicians. However, the challenge of ethnic variation needed to be addressed to improve the accuracy of automated algorithms. To achieve this, the authors concluded that there must be an increase in the quantity of available clinical data, which would require the active participation of local healthcare providers and the dermatological community. Blum *et al*. [38] discussed the advantages and potential risks of using artificial intelligence in dermato-oncology, particularly for skin cancer diagnosis and treatment. The advantages included increased efficiency and the ability for medical professionals to focus on patients, while the potential risks included a lack of trust and misclassification of benign

lesions. The work also mentioned that smartphone apps could be useful for disease-specific information, but they required clear guidelines and proper implementation. Mbunge *et al*. [32] proposed a systematic review on the use of TD and mHealth in South Africa during the COVID-19 pandemic. The researchers found that South Africa adopted various digital solutions based on mobile technology during the pandemic, including SMS services, messengers (for example, WhatsApp), mHealth apps, eHealth and telemedicine, AI, chatbots, and robotics. However, these technologies faced many obstacles, including managerial and financial barriers, legal and policy barriers, infrastructure and technology barriers, and cultural barriers. The authors recommended that energy be invested in community networks, especially in rural/remote areas, to modify mHealth policies, to develop sustainable strategies for the mobilization of resources, and to link accessible worldwide initiatives supporting this mobile technology.

The reviews considered herein identified the following opportunities and problems, in which AI was also considered an element:

OPPORTUNITIES

•TD and mHealth can provide access to specialized care and improve patient outcomes.

•TD and mHealth can increase access to healthcare resources, improving access to specialized centers for people living in remote areas.

•TD and mHealth can enable the early identification of patients through diagnoses of cutaneous signs.

•mHealth and AI can be useful in dermatology, particularly in African countries with limited medical care and long distances between patients and physicians.

•TD and mHealth can be useful for disease-specific information, screening, disease surveillance, medication compliance, and communication during pandemics.

•Incorporating digital dermatology into clinical practice can improve diagnostic accuracy and provide access to dermatological evaluations for underserved communities and those in rural settings.

PROBLEMS

•The adoption and implementation of TD and mHealth technologies, including those integrated with AI, face technical issues, legal frameworks, and regulatory barriers.

•Incorporating digital dermatology into clinical practice requires legal frameworks to be addressed and reimbursement policies to be updated to benefit patient care.

•Technical issues can negatively affect the adoption of TD and mHealth technologies.

•The challenge of ethnic variation needs to be addressed in order to improve the accuracy of automated algorithms.

•TD and mHealth technologies face infrastructural and technological barriers, organization and financial barriers, policy and regulatory barriers, as well as cultural barriers.

CONCLUSION

The topic explored in this overview, concerning the integration of Digital Dermatology and Telemedicine (TD) with mobile health (mHealth), is notably intricate. Both technologies have historically faced significant challenges when integrating into the healthcare domain.

Telemedicine inherits regulatory issues similar to telemedicine and e-Health, which were only partially addressed during the COVID-19 pandemic. The integration of mHealth, a relatively new technology in its connection with digital health imaging, primarily relies on smartphone applications. While it offers opportunities to reach a wider population, it also presents its own set of challenges.

The integration of mHealth with digital dermatology and TD has accelerated during the COVID-19 pandemic, providing new possibilities for citizens and healthcare stakeholders. This review aims to contribute by assessing the current state of integration in this field. Our study adopts a narrative review approach, particularly useful in emerging scientific fields with limited medical knowledge. Narrative reviews, alongside systematic reviews, play an essential role in building knowledge in these young sectors. In this narrative review, we formulated research questions, followed a standardized checklist, and employed a well-defined review process to connect the various specific issues addressed in this field.

The overview reveals several opportunities in this

area, accelerated by the urgency created during the COVID-19 pandemic. Moreover, evidence suggests that this technology was maturing even before the pandemic. By the end of 2018, with a significant portion of the global population having access to mobile phones, TD had the potential to be a valuable tool for diagnosis and management when integrated with mHealth. The integration of mHealth-based solutions into TD presents a novel paradigm in image diagnostics, enabling citizens to actively participate in their healthcare. Self-diagnosis apps have emerged across various categories in dermatology, including TD, self-surveillance, disease guidance, reference, dermoscopy, conferences, education, photograph storage, sharing, and journal apps. The ability for self-diagnosis in dermatology represents a significant technological advancement, with applications ranging from monitoring acne, vitiligo, psoriasis, and skin cancers. These opportunities extend to diverse populations, including young people, frail individuals, the elderly, and those in disadvantaged areas. The availability of robust client and server architectures for storing images also facilitates professional training in dermatology. Similarly to digital pathology, which allows remote access to electronic slides via smartphones, digital dermatology provides smartphone access to a repository of digital images, simplifying training and freeing up laboratories for more critical tasks.

The overview also highlights various challenges and barriers in this sector. While mobile devices have proliferated worldwide, the issue of the digital divide persists, particularly concerning infrastructure and devices in disadvantaged regions. Digital literacy, particularly among the elderly population, also poses a challenge. The central role of citizens in connecting to healthcare services transforms them into de facto operators/technologists. This places a substantial responsibility on app- and hardware-based smartphone tools, necessitating attention to aspects like cybersecurity, standardization, technological innovation, and ethics. In addition to mobile technology, artificial intelligence (AI) is emerging as a game-changer in healthcare. Integrating AI with TD and mHealth introduces new complexities, including issues of trust, time required for assessing benign lesions, insufficient medical knowledge for interpreting AI decisions, rapid follow-up in case of incorrect AI classifications, medico-legal concerns, reimbursement challenges, and limitations in providing adequate assistance based on AI-generated images. Moreover, various domains of intervention are emerging in this area, encompassing technologies and ethical considerations. By shifting the focus to decision-makers and diagnosticians, the overview underscores that challenges on the patient's side, such as image capturing issues, translate into difficulties for diagnosticians. The lack of guidelines, specific legislation, clear reimbursement procedures, and well-defined workflows further complicate the diagnostic process. Ultimately, the satisfaction of all actors in the mHealth process, including citizens, depends on the quality of images, ease of data upload, efficient data exchange, medical reimbursement, and medico-legal aspects.

As observed in the overview, artificial intelligence has made a significant contribution to TD and its integration with mHealth. This integration signifies a promising trajectory for future development. Challenges in this path, including regulatory and ethical aspects, mirror those in other imaging disciplines such as digital pathology and radiology. However, the active involvement of citizen-patients-operators necessitates unique attention in this integration process. Training AI algorithms to eliminate population bias, collecting more clinical data, and involving local healthcare providers and dermatological communities are crucial steps for enhancing AI's efficacy and usability in dermatology. Augmented reality presents another promising development area, with applications in patient-centric settings, medical education, training, and cosmetology. AR holds potential for improving education outcomes, enhancing dermatological condition measurement, and expanding clinical interventions. Wearable devices offer additional integration possibilities. These devices are increasingly empowering citizens to engage in virtual healthcare through interconnected tools.

In conclusion, the integration of mHealth, AI, AR, and wearable devices in TD and digital dermatology presents an attractive development scenario. Citizens, as active participants in monitoring and treatment processes, can connect with virtual healthcare through these integrated tools. However, addressing the complexities of integration requires collaborative efforts from scholars, healthcare professionals, and policy-

makers across various intervention domains. This collaborative approach is essential to ensure the responsible and effective integration of TD and mHealth into the healthcare ecosystem.

Authors' Contribution

Study Conception: ŞG; Study Design: ŞG; Supervision: ŞG; Funding: N/A; Materials: N/A; Data Collection and/or Processing: ŞG; Statistical Analysis and/or Data Interpretation: ŞG; Literature Review: ŞG; Manuscript Preparation: ŞG and Critical Review: ŞG.

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Therapeutic approaches to language skills in major neurodegenerative disorders: a literature review

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ABSTRACT

Major Neurodegenerative Disorders (MNDs) impact a large number of individuals globally. Individuals with neurodegenerative diseases have a significant problem due to the gradual development of communication difficulties. This is a review article to address the latest ways to manage and help individuals with language problems because of neurological diseases like Alzheimer's disease, mild cognitive impairment (MCI), and primary progressive aphasia (PPA). In the beginning we'll discuss the diseases, and then we'll be discussing how to treat them. The therapies used for Alzheimer's disease and PPA have been subject to extensive research. Therefore, the techniques follow a more structured way. However, there is a limited number of research in MCI and the strategies used in MCI mostly concentrate on enhancing the communication abilities of patients and their caregivers. There is a need for more research to increase approaches for speech and language therapy, as there is limited research on intervention in Turkish patients with MCI, PPA and Alzheimer's disease. It is critical to have evidence-based practice in MNDs, and more research is required to understand the effectiveness of speech and language therapy.

Keywords: Major neurodegenerative disorders, Alzheimer's disease, primary progressive aphasia, dementia, speech and language therapy

Major Neurodegenerative Disorders (MNDs) can be categorized based on their clinical symptoms, with extrapyramidal and pyramidal movement abnormalities, language deficits and cognitive or behavioral problems being the most prevalent [1]. Language difficulties are commonly seen in several neurodegenerative diseases, typically appearing as a prominent symptom in the early stages, as in the case of Primary Progressive Aphasia (PPA) [2]. Language impairments may also be present alongside other cognitive problems, as shown in Alzheimer's disease (AD) [3]. Recent developments in our comprehension of the neuroscience of language have led to the revision of certain initial concepts about language recovery.

In clinical application, there are limited studies and reviews on people with MND and the speech therapy approaches that are generally used with them. So, it is very important to understand the difficulties that they have and to manage their situations. People with MND need to have speech and language therapy to preserve their speech and language abilities. Speech-language therapy is tailored to address the specific needs of these individuals. When individuals are im-

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pacted by MND, they exhibit a gradual decline in many abilities, with a significant focus on speech and language function.

This review examines the current treatment and intervention strategies for language difficulties caused by MNDs such as AD, MCI, and PPA. Firstly, we will start by explaining the diseases and then the therapy approaches will be outlined.

MILD COGNITIVE IMPAIRMENT (MCI)

MCI is a defined condition characterized by cognitive deterioration that exceeds what is often predicted for an individual's age and level of education, but does not significantly interfere with their everyday activities. Therefore, it is different from dementia, since dementia involves more severe and extensive cognitive deficits that significantly impact everyday functioning [4].

Petersen *et al*. [5] were the first to establish specific criteria for diagnosing MCI. The criteria for diagnosis are as follows: (a) subjective complaint of memory loss, (b) objective impairment of cognitive capacity, (c) preserved general cognitive function, (d) intact activities of daily life, (e) person does not fulfill criteria for dementia. Individuals who fulfill these specific requirements have a higher likelihood of getting Alzheimer's disease compared to the general population [5, 6].

For MCI assessment, the following six areas of cognition were chosen for examination: language, visual-spatial construction ability, learning and memory, complex attention, social cognition, and executive function [7]. As the language is a significant domain in MCI, Speech-language pathologists (SLPs) are very important for assessing and treating patients with MCI. They are responsible for providing cognitive-communication training or rehabilitation to patients with MCI.

The most often reported language performance impairment in patients with MCI is a decline in verbal fluency, which is assessed by asking individuals to list as many objects as they can within a certain category [8-10]. Also, when confrontational naming was assessed, it was evident that they have difficulty in naming objects, famous people and buildings [11]. It is very important to notice and determine the changes in language characteristics of MCI patients and create specific therapeutic programs for them.

There are limited studies in the Turkish language conducted with Turkish speaking MCI patients [12]. As a result of their study, they found that nonword repetition test and narrative comprehension, and story grammar scores were significantly different between a MCI patient and healthy aging participants.

Traditionally, language intervention has aimed to enhance the communication skills of individuals. Language difficulties are a substantial problem for most individuals with MNDs, especially as the condition progresses. Initial indicators of communication impairment appear as challenges in word retrieval, especially with terms associated with known individuals or items [13].

Assessment and speech-language therapy for MCI can be varied according to the patients and their daily lives. There are some specific language therapy options, speech-language therapists (SLTs) can offer cognitive-communication training or rehabilitation to individuals with MCI and early-stage dementia caused by AD. Speech and language therapy aims to assist patients in managing their condition, enhancing their functional abilities, improving their quality of life, and preparing them for future decline. [14, 15]. Recent research indicates that cognitive rehabilitation may extend the duration of independence in patients with MCI [16]. Many individuals with dementia reside in their home environment and get aid and supervision from caregivers. Therefore, it is better to educate patients' caregivers and provide counseling activities to patients with MCI or dementia who are residing in the community [17].

Also, engaging in discussions about long-term planning is crucial for all patients, particularly older adults, and especially those who may be dealing with a progressive illness. This ensures that their care aligns with their desired outcomes. The primary responsibility for conducting these discussions will usually fall on the patient's primary care clinician or social worker, while the SLT can provide valuable assistance and support.

SLTs have access to several methods to assist patients in properly expressing their desires. They might also use strategic planning as part of their therapeutic objectives. Given that the patient resides in the community, the objectives should prioritize enhancing safety within their home environment and facilitating

their normal activities. Goals may also prioritize the development of augmentative and alternative communication (AAC) techniques, such as Memory Books. Initiating the creation of mnemonic devices at an early stage can perhaps alleviate the apprehensions of individuals who are apprehensive about their future memory and communication abilities. Formal dementia-based caregiver training programs can be beneficial for caregivers, such as family members and friends, since they provide assistance for readiness and long-term care. SLTs can also assist by offering communication partner training.

While the SLT does not have the responsibility to directly treat psychological conditions, it is suitable and beneficial for the SLT to anticipate and recognize these emotions. The SLT should create a secure environment for the patient to express their feelings, particularly when they are related to their cognitive-communication objectives. Additionally, the SLT should be aware of when and where to refer the patient for assistance. SLTs can assist the patient in addressing grief by working together to establish cognitive-communication objectives that prioritize reducing distress and enhancing resilience, functionality, safety, and purposeful existence.

ALZHEIMER's DISEASE (AD)

Cognitive-communication impairments are a significant feature of AD, and communication difficulties can arise as early as the first stage of the condition [18]. Impairments in the areas of language comprehension and expression are associated with memory and other forms of cognitive decline [19]. According to Bayles *et al*. [20], the cognitive communication problem that occurs in AD is characterized by severe deficiencies in identifying, describing, writing, and pragmatics. These deficits are dependent on the progression of the disease. The deterioration of this language seems to follow a hierarchical pattern, where the language forms that are learnt last in the order of language development deteriorate first [21].

In the early-stages of dementia caused by AD, language abilities and other cognitive abilities are addressed in order to assist patients in managing their condition, optimizing their functional abilities, enhancing their quality of life, and preparing for future deterioration [14, 15]. Early stages are distinguished by anomia repetitions, and periphrasis, whereas aphasic-like language develops later in the course of the disease [22]. Semantic mistakes (e.g. trouble choosing the right word, limited vocabulary) are common [23], and semantic [24] and letter fluency [25] issues may be noticed. As the disease progresses, all language modalities are affected.

Morello *et al*. [26] investigated the impacts of non-pharmacological interventions on individuals with AD. Their study results indicated that lexical-semantic approaches and treatments that target multiple cognitive domains, including language, are potentially efficacious. Recent research has shown significant advantages of language rehabilitation on its own, as well as when combined with other cognitive activities. The studies that demonstrated more significant improvements were the ones that employed comprehensive language-cognitive intervention programs [27-30].

The limited amount of data on dedicated language rehabilitation may be attributed to the lack of research that specifically targets language therapy and compares them to broad cognitive interventions. Future research should prioritize the investigation of exclusive language rehabilitation and the comparison of language and cognitive therapy methodologies.

PRIMER PROGRESSIVE APHASIA (PPA)

PPA is a subtype of dementia that is characterized by a decline in language skills while memory remains relatively intact. Over an extended period, the primary indications and manifestations may be limited to the domain of language [31]. PPA refers to a collection of neurological conditions characterized by significant speech and language impairment [32]. The language problem seen in individuals with PPA may present as agrammatic, logopenic, or semantic aphasia, which is determined by the specific anatomical distribution of cortical atrophy [33].

This syndrome is characterized by a language disorder that originates from neurodegeneration and manifests relatively independently of other significant neurological symptoms for the initial one to two years following onset. Furthermore, this disorder maintains its predominance for the majority of the disease trajectory. The onset typically arises prior to the age of

65, and its prevalence is roughly equivalent between the sexes [33].

Three variants of PPA have been identified as (1) agrammatic (PPA-G), (2) semantic (PPA-S), and (3) logopenic according to the nature of the language impairment; each is associated with a clinically consistent distribution of peak cortical atrophy [34, 35]. The subtypes of PPA are as follows [36]:

1. PPA-G: PPA with agrammatism refers to a condition marked by slow and difficult speech, difficulty in producing and/or understanding grammatically correct sentences, and varying levels of difficulty in recalling words, with some ability to understand individual words remaining intact. Comprehension of sentences is hindered when dealing with highly challenging morphosyntactic structures, such as negative passives and clauses with negative objects.

2. PPA-S: In this variety, it is typical to observe semantic paraphasias, which refer to the substitution of a more familiar exemplar within the same category. For example, the word "dog" may be used instead of "hyena". During the early phase, the abilities to articulate, understand and produce sounds, organize sentence structure, and repeat information are preserved. As the condition advances, the ability to produce language may become "vacant", lacking in nouns and mostly consisting of imprecise placeholders like "thing", as well as function words like "this" or "the". The ability to spontaneously name items is significantly decreased, and typically, providing several choices does not lead to improved performance.

3. PPA-L: PPA has also been associated with "logopenic" language output, which is characterized by problems in choosing words and decreased output. This type of language output is syntactically simple yet correct. This variety is characterized by phonemic paraphasias, which refer to the substitution of sounds within single words, such as saying "tamp" instead of "lamp".

Significant advancements have been achieved by speech and language therapists (SLTs) in comprehending the broader ramifications of these communication challenges on the quality of life, interpersonal connections, and daily functioning of individuals with PPA [37]. This has influenced the development of a number of crucial intervention strategies and the speech and language therapy literature, such as lexical retrieval therapies, script therapy, communication partner training, communication aides, and multimodal communication therapy [38].

Volkmer *et al*. [32] suggested that impairment-based approaches, compensatory-based approaches, group education and support and therapeutic models – heading to a person-centered approach can be used for patients with PPA. Impairment-based methods use particular techniques for word retrieval, including semantic feature analysis and phonemic component analysis. In addition, script training may also be used as a therapeutic strategy to assist individuals with PPA-G. Additionally, individuals with PPA may benefit from the use of alternative and augmentative treatment approaches. These strategies are very effective in facilitating communication in daily life activities and provide patients with a means to express themselves. When it comes to providing opportunities for socialization, group treatments are quite beneficial, and speech therapy techniques that are especially customized to the individual are also highly significant. Individuals who have PPA may benefit from using the Life Participation Approach for Aphasia [39] as a framework to develop therapeutic goals for them.

CONCLUSION

Speech, language, and communication problems are experienced by people with MCI, PPA, and AD, as well as their carepartners. These challenges have a detrimental effect on the individuals' ability to participate in social activities and their mental health. Dementia-related disorders are progressive and require individualized interventions to optimize cognitive and communicative functioning throughout the disease course [40].

Recommendations for speech and language therapy treatments should be made on a regular basis for individuals who have MND. A wide range of therapies may be provided by speech and language therapists in order to adjust the needs of individuals who have MND and the families of those individuals. During speech and language therapies, different approaches can be used such as impairment based approaches, family counseling and partner training and alternative augmentative communication.

Further investigation is necessary in this field to substantiate the clinical practice of SLTs and improve

the quality of life for patients. Also, evidence-based practice manuals are particularly required to be effective in clinical settings.

Authors' Contribution

Study Conception: FSK, ST, NÇ; Study Design: FSK, ST, NÇ; Supervision: FSK, ST, NÇ; Funding: FSK, ST, NÇ; Materials: FSK, ST, NÇ; Data Collection and/or Processing: FSK, ST, NÇ; Statistical Analysis and/or Data Interpretation: FSK, ST, NÇ; Literature Review: FSK, ST, NÇ; Manuscript Preparation: FSK, ST, NÇ and Critical Review: FSK, ST, NÇ.

Conflict of interest

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Clinical and genetic diagnosis of two Turkish patients with hereditary spherocytosis

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ABSTRACT

Hereditary spherocytosis is a congenital disorder caused by defects in the erythrocyte membrane. It is characterized by hemolytic anemia, jaundice, splenomegaly, and cholelithiasis. The clinical presentation is variable. Especially in the neonatal period and cases without a family history, it isn't easy to diagnose with classical approaches. Here, we describe the genetic findings of a 1.5-month-old and a 2-month-old girl diagnosed with hereditary spherocytosis in Turkish families. Both cases presented with severe anemia and jaundice. Spherocytes were frequently seen in peripheral blood smears. Targeted next-generation sequencing (NGS) revealed that the 1.5-month-old girl was heterozygous for a novel frameshift mutation c.1617del (p.Leu540CysfsTer31) in exon 15 of the ANK1 gene, while the 2-month-old girl was heterozygous for a mutation c.1912C>T (p.Arg638Ter) in exon 13 of the SPTB gene, which leads to abnormal protein truncation. Parents did not carry these mutations. To our knowledge, the ANK1 mutation identified in a 7-month-old girl has not been reported previously. NGS may be helpful in diagnosing hereditary spherocytosis, especially in atypical cases.

Keywords: Hereditary spherocytosis, hemolytic anemia, neonatal jaundice, gene mutation

Hereditary spherocytosis (HS) is the most common inherited hemolytic anemia caused by gene mutations encoding erythrocyte cell membrane and skeletal proteins [1]. The prevalence of HS, which occurs in all racial groups and is especially common in individuals of Northern European origin, is reported as one case in 2000-3000 individuals [1, 2]. The prevalence in Turkey is unknown [3]. The clinical manifestations of HS are highly variable, ranging from almost asymptomatic disease to life-threatening anemia, severe splenomegaly, and/or severe bilirubinemia, even within the same family [2, 4, 5]. HS is most commonly associated with dominant inheritance (75%). The remaining cases represent autosomal recessive (OR) inheritance or de novo mutations in some sporadic cases [4, 5, 6]. HS is caused by defects in erythrocyte membrane proteins, including ankyrin, band 3, alpha-spectrin, beta-spectrin, and protein 4.2, encoded by the *ANK1, SLC4A1, SPTA1, SPTB,* and *EBP42* genes, respectively [7, 8]. *ANK1* and *SPTB* mutations constitute the most common causes of typical autosomal dominant HS, while autosomal recessive inheritance frequently involves *SPTA1* and *EBP42* gene variants [8, 9]. De novo *ANK1* and *SPTB* variants are relatively rare in HS [7, 9]. In this report, we have identified, through next-generation sequencing (NGS), a novel *ANK1* frameshift mutation causing HS in the first case and an *SPTB* mutation leading to abnormal truncation of the protein previously described in the literature in the second case.

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CASE PRESENTATION

Case 1

A 1.5-month-old baby girl with no other known disease was admitted with the complaint of decreased sucking and jaundice. The baby was born as a monozygotic twin at 34 weeks of gestation, weighing 2030 grams, and received phototherapy treatment after birth and erythrocyte suspension twice during her 3-week follow-up in the neonatal intensive care unit. There was no consanguinity between the parents, and there was no other blood disease in their family. Physical examination revealed pallor of the skin and icterus in the sclera. Laboratory investigations revealed moderate anemia, reticulocytosis, and indirect hyperbilirubinemia on a complete blood count. A peripheral smear was evaluated, and there was no significant increase in spherocytes. The direct Coombs test was negative. Hemoglobin electrophoresis revealed no abnormal hemoglobin variant. At 10 days of age, the os-

Table 1. Laboratory findings in Turkish cases with hereditary spherocytosis

Characteristics	Case 1	Case 2
Hemoglobin (g/dL) (reference range: 9.2-11.4)	5.9	7
MCV (fL) (reference range: 83.4-96.4)	82.7	85.8
MCH (pg) (reference range: 28-32.5)	27.6	29.5
MCHC (g/dL) (reference range: 32.5-34.9)	33.3	34.4
RBC ($\times 10^6$/ µL) (reference range: 2.9-3.8)	2.14	2.54
Reticulocytes (%) (reference range: 0.5-2)	12.76	4.28
Absolute reticulocyte count ($\times 10^9$/L), (reference range: 50-100)	273	109
Direct Coombs	Negative	Negative
Total bilirubin (mg/dL) (reference range: 0.3-1.2)	12.6	2.47
Direct bilirubin (mg/dL) (reference range: 0-0.2)	0.98	0.51
Serum iron (µg/dL) (reference range: 27-159)	114	71
Ferritin (µg/L) (reference range: 10-200)	179	197
Lactate dehydrogenase (U/L) (reference range: 0-247)	287	241
Glucose 6 phosphate dehydrogenase (U/g Hb) (reference range: 7-21)	13.6	10.3
Pyruvate kinase (U/g Hb) (reference range: 111-406)	267.4	389.9

MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration MCV=mean corpuscular volume, RBC=red blood cell.

motic fragility test (OFT) result was negative. The glucose-6 phosphate dehydrogenase and pyruvate kinase enzyme levels were within normal limits (Table 1). Alpha and beta-globin genetic analyses excluded alpha and beta-thalassemia. Abdominal ultrasonography showed no splenomegaly. Genetic analysis was performed by NGS to determine the cause of unexplained hemolysis. Genetic analysis revealed that she was heterozygous for a c.1617del (p.Leu540CysfsTer31) frameshift mutation in exon 15 of the *ANK1* gene. It was determined that neither of her parents carried this mutation. Our patient received her first transfusion at 12 days of age and has required a total of 6 red blood cell transfusions to date. Our patient is now 1.5 years old, and the last red blood cell transfusion was given at 14 months of age. Initially, an average of one transfusion per month was performed, and the transfusion rates gradually decreased during follow-up. Her hemoglobin levels have ranged between 9 g/dL and 10 g/dL. She is receiving folate supplements and is being followed up intermittently in our clinic with supportive measures without a splenectomy.

Case 2

A term infant with a birth weight of 3000 grams was admitted on the 2nd postnatal day because of skin jaundice. There was no consanguinity between the parents, and there was no family history of hereditary hematologic disease. Investigations revealed anemia and reticulocytosis. The direct Coombs test was negative. Total bilirubin was 22.5 mg/dL and direct bilirubin was 0.7 mg/dL, and she was hospitalized in the neonatal intensive care unit because of indirect hyperbilirubinemia. Phototherapy treatment was started. In the follow-up, Hb decreased to 7 g/dl, and erythrocyte suspension was given. The glucose-6 phosphate dehydrogenase and pyruvate kinase levels were normal. No abnormal variant was found on hemoglobin electrophoresis. A peripheral smear showed few spherocytes, polychromasia, and rare nucleated red blood cells. At 7 days of age, the OFT test result was negative (Table 1). Abdominal ultrasonography showed no splenomegaly. NGS of genomic DNA obtained using periferic blood samples demonstrated heterozygosity for SPTBc.1912C>T (p.Arg638Ter). Her parents were screened for mutations, and none of them had mutations. The first blood transfusion was performed at 15 days of age in the neonatal period, and a total of 13 times red blood cells were administered. Our patient is now 3 years old, and the last red blood cell transfusion was given at 30 months of age. Initially, blood transfusion requirements were more frequent, but transfusions' frequency gradually decreased during follow-up, and Hb levels ranged between 9 g/dL and 10 g/dL. Folic acid supplementation is continued.

DISCUSSION

Hereditary spherocytosis is rarely encountered in the neonatal period, and the diagnosis might become difficult if there is no known family history [8, 10]. Here, we describe two cases with no family history, one confirmed by NGS in the *ANK1* gene and the other in the *SPTB* gene.

Hereditary spherocytosis is usually diagnosed in childhood. Anemia, jaundice, and splenomegaly are the main clinical features [5, 11]. The diagnosis is usually made on clinical suspicion, including family history and typical biological signs of HS (increased MCHC>36 g/dL, spherocytic cells in blood smears, non-immune hemolytic anemia, positive osmotic fragility test) [5, 12, 13]. Although increased spherocytes in the blood smear are useful in the diagnosis of HS, they can also be seen in immune hemolytic anemia, sepsis, ABO incompatibility, and glucose-6 phosphate dehydrogenase enzyme deficiency [5, 10, 14]. In addition, approximately 10% of patients with HS may not have spherocytes in the peripheral smear, and as a result, may be misdiagnosed [11]. Furthermore, although the OFT test is a confirmatory test for diagnosing HS, its sensitivity and specificity are low [14]. False-negative results may be observed in OFT tests in patients with iron deficiency and obstructive jaundice. The OFT test may also be false positive in hereditary elliptocytosis and autoimmune hemolytic anemia [10, 14, 15]. The OFT test also has some pitfalls when used in neonates. In neonates, HS erythrocytes are more sensitive to osmotic lysis than normal erythrocytes due to the reduced membrane surface area. Therefore, it is recommended to use neonatal osmotic fragility curves instead of adult curves. In addition, the OFT test can't distinguish spherocytes seen in HS from spherocytes resulting from other causes, such as ABO incompatibility [16, 17]. In cases with an atypical course and no family history of HS, genetic studies

identify the clinical presentation of hereditary blood diseases [6, 11, 13]. The two cases in our study have had unexplained hemolysis and indirect hyperbilirubinemia since the neonatal period. There was no family history. OFT tests were negative. The glucose-6 phosphate dehydrogenase and pyruvate kinase tests were negative. Therefore, we used the NGS panel to identify the responsible genes for hematologic disorders in these patients. In our first patient, we found a de novo *ANK1* c.1617del (p.Leu540CysfsTer31) frameshift mutation, which had not been previously described in the literature. In the other patient, we detected the *SPTB* c.1912C>T (p.Arg638Ter) mutation previously defined in the literature and reached the diagnosis this way [18, 19].

Molecular genetic testing can be used as an effective way to reach an accurate clinical diagnosis. For this purpose, NGS-based genetic tests have provided an alternative to conventional tests, especially in the diagnosis of genetic disorders showing phenotypic and genetic heterogeneity, and the use of the tests has begun to increase gradually [10, 20].

Five genes have been identified as responsible for HS (*SPTA1, SPTB, ANK1, SLC4A1*, and *EPB42*) (4, 15). *ANK1* mutations are the most common among this group and account for approximately half of all HS. Park *et al*. [21] confirmed that heterozygous *ANK1* mutations account for 52% of all Korean patients. Nakanishi *et al*. [22] found that *ANK1* mutations are involved in approximately 31% of Japanese HS patients. The majority of reported mutations, including nonsense, end-joining, and frameshift mutations, were predicted to result in protein truncation [1, 10]. More than 60 mutations have been identified in *ANK1* [23]. However, this is the first case of HS caused by a frameshift mutation in exon 15 of the *ANK1* gene.

Another protein that plays an important role in erythrocyte membrane stability is beta-spectrin encoded by the *SPTB* gene [23]. The *SPTB* mutation is the second most common pathologic mutation in HS after the *ANK1* mutation, and this mutation is responsible for approximately 20% of HS cases [1, 12]. In a Korean study, 25 patients with HS were reported to carry mutations in *ANK1* (n=13) or *SPTB* (n=12). In another study conducted in China, 13 mutations in *ANK1* and 10 mutations in *SPTB* were observed in 23 patients. In a study conducted in Japan, *ANK1* variants were the most common and were observed in 46% (6/13) of patients, while *SPTB* variants were identified in 31% (4/13). To date, most gene defects in *SPTB* (splicing, nonsense variants, and frameshift variants) usually result in exon skipping, mRNA transcript instability, or truncated synthesis of beta-spectrin proteins [7, 99. In a recent study, 6 frameshift, 5 nonsense, and 1 insertion error mutations were reported in the SPTB gene [12]. In the second case, we described a mutation that abnormally shortens the protein in the 13th exon of the *SPTB* gene, which was previously reported in the literature.

The genotype-phenotype correlation of HS is currently unclear [10, 13]. The complexity of mutations and gene regulation may explain the heterogeneity of clinical manifestations [13]. Patients with *ANK1* gene mutations are more prone to anemia and have a higher reticulocyte count compared to those without this mutation. Clinical findings may also vary according to ANK1 mutation sites. It has been suggested that spectrin-binding or regulatory mutations in the *ANK1* gene may be associated with more severe anemia. However, co-inheritance of mutations in iron and bilirubin metabolism and erythrocyte defects may affect phenotypic variability in HS. This phenotypic variability may depend on age and race [24]. As a result, the severity of the disease may differ between individuals even if the site is the same [10, 13]. Therefore, we should combine clinical, erythrocyte morphology, biochemical, and genomic data in the diagnosis of HS [23]. In this article, we demonstrated two different mutations that may explain the clinical picture in two patients with no family history, who received the first transfusion in the neonatal period and continued to require transfusion in the follow-up. Although severe anemia was observed in the early period in both patients, the frequency of transfusion decreased with age.

Because of HS's phenotypic and genetic heterogeneity, it is difficult to diagnose, especially in atypical cases. Genetic diagnosis has gained more importance since traditional diagnostic tests miss the diagnosis of HS due to late results.

The NGS method is now becoming prominent in suspected erythrocyte membrane disorders, both in terms of reaching a diagnosis in a shorter time and in terms of efficiency, and the use of NGS is becoming increasingly widespread [11, 13, 14]. This genetic technology also provides information for potential ge-

netic counseling and future research [13, 14].

The first line of treatment is supportive care. Phototherapy is often given to newborns, and transfusions are given in severe cases. In the older age group, blood transfusions may be required during hemolytic crises. Splenectomy may be useful in cases of HS and prolongs the life span of erythrocytes [4, 13]. However, the risk of infection is a disadvantage of splenectomy in childhood. The diagnosis should be confirmed by a genetic diagnosis before splenectomy. In addition, folate supplementation is recommended for moderate-to-severe forms of HS [20]. Both of our patients received phototherapy treatment, and erythrocyte suspension support in the neonatal period and folate treatment was started in both cases.

CONCLUSION

In conclusion, mutations related to HS were identified, and the diagnosis was reached in two patients who had no family history and had required intermittent blood transfusions since the neonatal period. The lack of traditional diagnostic methods, especially in newborns with unclear clinical features and no family history, shows that the use of NGS is necessary for diagnosis. Molecular diagnosis and genetic counseling can predict the prognosis of young patients with HS.

Informed Consent

Parents were informed about the purpose of the case report, and informed consent was obtained from both families for this publication.

Authors' Contribution

Study Conception: ÇC; Study Design: ÇC; Supervision: ÇC; Funding: N/A; Materials: N/A; Data Collection and/or Processing: ÇC; Statistical Analysis and/or Data Interpretation: ÇC; Literature Review: ÇC; Manuscript Preparation: ÇC and Critical Review: ÇC.

Conflict of interest

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